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SERUM BILIRUBIN LEVELS IN THE NEWBORN INFANT

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THE recent demonstration of the value of serum bilirubin measurements in guiding the management of infants with erythroblastosis[1, 2, 3, 4] has made it desirable to compare the bilirubin elevations of erythroblastosis with those of physiological jaundice in the newborn period.

Numerous investigators have studied the problems of physiological jaundice.[5-14] Ross,[15] Waugh,[16] Davidson,[17] Weech,[18] Findlay,[19] Fashena,[20] and Halbrecht[21] have reported on the serum bilirubin of full-term infants, and Findlay[19] has investigated bilirubin levels in a few premature infants. Findlay agrees with Smith's clinical impression that physiological jaundice is more prolonged and more severe in premature infants.[22]

In their investigation of jaundice in normal newborn babies, Fashena[20] and Wexler and Wiener[23] showed that physiological icterus was unrelated to differences between baby and mother in respect to their blood groups. Serum bilirubin levels in erythroblastosis have been reported by Halbrecht[24] who showed elevation of cord serum bilirubin levels in "icterus precox," and Mollison[2] who obtained increased levels in infants with Rh incompatibility.

The present study was undertaken to obtain data with regard to the range of cord serum bilirubin levels and the range of daily bilirubin levels in full-term infants, premature infants, and infants with erythroblastosis fetalis.

MATERIALS AND METHODS

The clinical material consisted of infants seen at the Beth Israel Hospital, the Boston Lying-in Hospital, and the Children's Medical Center, Boston. The normal infants were delivered at term, weighed more than 2,500 grams at birth, and were selected at random. The premature infants included those who weighed less than 2,250 grams at birth regardless of the gestational age; these were consecutive cases. The infants were classified by the Blood Grouping Laboratory of the Children's Medical Center as follows: (1) "compatible"—no A, B, or Rh incompatibility between infant and mother; (2) "incompatible"—A or B incompatibility between infant and mother with no evidence of erythroblastosis in the infant; (3) erythroblastosis—definite evidence of hemolytic disease in the infant and sensitization in the mother.

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(The erythroblastotic infants were not selected, but had somewhat higher average bilirubin levels than would be seen in a random group since only the more severe cases are referred to the hospital.)

The serum bilirubin levels were determined by the method of Hsia, Hsia, and Gellis[25] from capillary blood using either 0.05 or 1.0 c.c. of serum. With this method, it was possible to obtain satisfactory samples at frequent intervals without undue trauma to the infant. Determinations were done daily on full-term infants for five days and on premature infants until the bilirubin level fell below 2 mg. per cent. Although both the one-minute and total serum bilirubin may be done satisfactorily with the method employed, the one-minute reading was omitted because it has been found to be within normal limits in physiological jaundice and in erythroblastosis.

RESULTS

Table I shows the average, the maximum, and the minimum bilirubin levels in cord blood of: (1) full-term compatible infants, (2) full-term incompatible infants without evidence of sensitization, (3) premature compatible infants, and (4) infants with erythroblastosis fetalis. There is no significant difference between the levels of the compatible and incompatible full-term infants. The premature infants appear to have somewhat lower levels than the full-term infants, but the series is too small to make the dif-

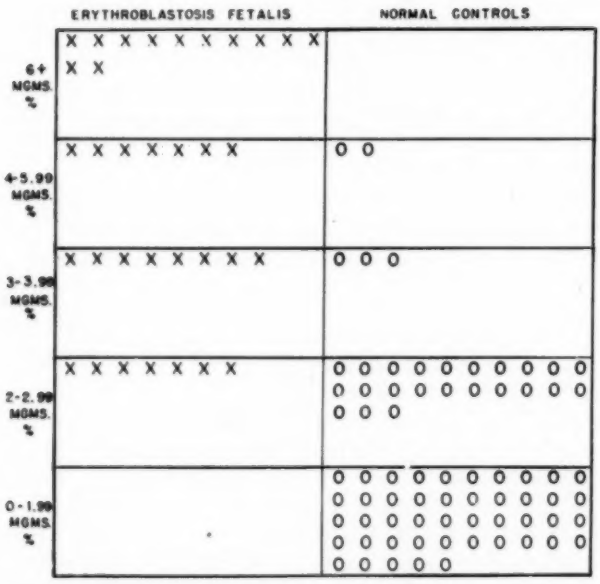

Fig. 1.—Each "X" represents the cord serum bilirubin level in a single baby with erythroblastosis. Each "O" represents a single normal baby. (From Hsia, Allen, Gellis, and Diamond: New England J. Med. 247: 668, 1952.)

ference significant. The infants with erythroblastosis have an average level considerably higher than that of normal infants. However, if examined in terms of specific values, there is some overlapping between the two groups as shown in Fig. 1.

Tables II and III show the daily serial bilirubin determinations in full-term compatible and incompatible infants (all normal). It can be seen that there is no significant difference between these two groups. In both groups, the peak of serum bilirubin

TABLE I. TOTAL BILIRUBIN LEVELS IN CORD BLOOD SERUM IN VARIOUS GROUPS OF INFANTS. THE VALUES ARE EXPRESSED AS MILLIGRAMS PER 100 C.C. SERUM

	AVERAGE	MAXIMUM	MINIMUM
45 normal full-term "compatible" infants	1.8	3.9	0.9
44 normal full-term "incompatible" infants	2.0	5.9	0.2
9 premature infants	1.3	2.9	0.0
34 infants with erythroblastosis fetalis	5.1	10.3	2.1

TABLE II. DAILY TOTAL SERUM BILIRUBIN LEVELS IN FULL-TERM "COMPATIBLE" INFANTS. VALUES ARE EXPRESSED AS MILLIGRAMS PER 100 C.C. SERUM

BABY	CORD BLOOD	1 DA.	2 DA.	3 DA.	4 DA.	5 DA.	BLOOD GROUPS	
							MOTHER	BABY
Sim	1.6	7.4 (20)	12.4	13.2	12.3	9.5	AB	A
Man	2.5	6.9 (21)	10.3	9.2	7.2	4.7	O	O
Way	2.0	5.0 (17)	7.9	10.2	6.7	4.3	O	O
Sma	2.4	6.8 (14)	8.9	9.7	7.3	6.4	A	A
Gol	3.2	7.3 (31)	7.3	9.6	6.9	4.6	A	A
Kra	1.8	----	7.9 (49)	7.4	5.8	4.6	AB	A
Bra	1.5	4.9 (25)	6.9	5.6	5.2	3.2	O	O
Pen	1.4	5.2 (29)	6.0	3.8	1.7	1.5	O	O
Edw	3.1	5.2 (31)	6.0	5.0	2.7	2.2	O	O
Bah	1.8	6.2 (24)	3.1	1.8	1.0	--	A	A
Gra	2.2	4.0 (18)	4.4	3.6	1.5	0.9	B	O
Ros	2.5	3.4 (19)	4.1	0.6	0.0	--	O	O
Average bilirubin	2.2	5.7	7.1	6.6	4.9			
Average age (hr.)		23	47	71	95			

Figures in parentheses indicate age of the infant when the first postnatal sample was drawn. Subsequent samples were always taken at twenty-four-hour intervals.

TABLE III. DAILY TOTAL SERUM BILIRUBIN LEVELS IN FULL-TERM "INCOMPATIBLE" INFANTS. VALUES ARE EXPRESSED AS MILLIGRAMS PER 100 C.C. SERUM

BABY	CORD BLOOD	1 DA.	2 DA.	3 DA.	4 DA.	5 DA.	BLOOD GROUPS	
							MOTHER	BABY
Sim	2.5	5.2 (14)	7.9	10.9	11.9	10.6	O	A
Aro	5.0	------	11.6 (44)	11.6	9.8	8.4	O	A
Dar	2.5	10.4 (34)	9.5	6.1	4.4	2.8	O	B
Rob	1.9	8.1 (27)	9.2	9.3	7.1	3.1	O	A
Har	--	7.2 (13)	7.6	5.7	3.3	3.5	O	A
Tra	1.1	6.1 (23)	7.6	5.1	1.2	--	B	AB
Kap	--	------	6.9 (46)	5.6	5.2	1.5	O	B
Fri	2.0	4.6 (32)	5.4	6.4	4.4	3.2	A	AB
Lev	0.6	5.0 (13)	5.2	4.0	2.3	--	O	B
Abr	1.2	4.0 (24)	3.8	3.2	1.8	0.3	O	A
Kan	1.2	2.9 (24)	3.3	1.4	1.5	--	O	B
Spe	--	3.0 (18)	0.0	0.0	1.2	--	O	A
Average bilirubin	2.0	5.7	6.5	5.8	4.5			
Average age (hr.)		22	46	70	94			

Figures in parentheses indicate the age of the infant when the first postnatal sample was drawn. Subsequent samples were always taken at twenty-four-hour intervals.

TABLE IV. DAILY TOTAL SERUM BILIRUBIN DETERMINATIONS IN PREMATURE INFANTS. VALUES ARE EXPRESSED AS MILLIGRAMS PER 100 C.C. SERUM

	GEST. (WK.)	WEIGHT (GM.)	"BIRTH"	1 DA.	2 DA.	3 DA.	4 DA.	5 DA.	6 DA.	7 DA.	8 DA.	9 DA.	10 DA.	11 DA.
Hen	33	2015	1.1 (0)	9.5 (33)	12.4	21.6	27.0	21.3	19.8	15.6	13.3	9.7	8.0	6.8
Spi	35	1530	2.2 (0)	10.3 (34)	15.3	18.4	19.5	14.6	12.7	10.0	7.9	4.7	---	---
Ger	28	1640	2.1 (8)	6.1 (32)	11.8	15.6	16.1	16.5	15.7	12.9	12.9	10.9	9.2	7.9
Sto	36	2240	1.1 (0)	---	6.1 (52)	11.0	16.0	16.4	14.8	11.6	12.2	8.9	1.0	---
Rud	33	1815	--	6.6 (35)	8.6	15.5	16.3	10.5	9.0	8.3	6.8	5.7	---	---
Wei	35	1560	--	3.1 (12)	6.8	14.6	11.6	9.1	7.0	5.2	3.6	---	---	---
Bre	33	2015	1.4 (0)	5.9 (30)	11.2	14.0	11.0	9.2	9.6	7.9	8.4	7.4	6.2	5.2
Ise	31	1475	1.1 (0)	6.4 (24)	9.3	11.6	13.6	11.4	8.0	6.7	4.7	2.9	---	---
Web	39	2185	2.9 (0)	7.3 (28)	12.2	12.8	10.6	7.9	6.9	---	---	---	---	---
Bak	34	1900	0.0 (0)	---	6.9 (38)	8.6	12.7	12.0	9.5	8.4	4.8	3.6	1.8	---
Hei	34	2015	1.7 (0)	7.9 (25)	10.0	9.6	4.0	4.4	2.7	---	---	---	---	---
Jon	32	2185	--	4.1 (22)	6.9	5.2	8.2	0.7	1.9	---	---	---	---	---
Don	37	1815	0.4 (7)	1.2 (31)	2.7	1.1	0.3	---	---	---	---	---	---	---
Ess	39	2155	0.9 (5)	1.9 (29)	0.9	1.7	0.6	---	---	---	---	---	---	---
Mac	41	2240	0.0 (0)	0.0 (31)	0.0	0.0	---	---	---	---	---	---	---	---
Average 15 premature infants under 2,250 grams			1.3	5.4	8.1	10.7	11.2							
Average age (hr.)				27	51	75	99							
Average 11 premature infants less than 37 weeks of gestation			1.2	6.7	9.6	13.2	14.2							
Average age (hr.)				26	50	74	98							

(0) signifies cord blood. Other figures in parentheses indicate the age of the infant when postnatal samples were drawn. Subsequent samples were always drawn at twenty-four-hour intervals.

occurred, on the average, at about 2 days of age.

Table IV gives the data on fifteen premature infants. There is little difference between the premature group and the full-term infants with regard to serum bilirubin levels of the first and second days of life. However, the peak bilirubin of the premature infants occurs, on the average, on the fourth day of life in contrast to the peak bilirubin of full-term infants which occurs at two days. Bilirubin values in premature infants on the third, fourth, or fifth day of life are sometimes far above the range seen in normal full-term infants. These high values are in the range seen in infants with the hyperbilirubinemia of erythroblastosis fetalis. The data also suggest that immaturity in terms of gestational age is more important than the size of the baby in determining hyperbilirubinemia.

Table V shows bilirubin levels in infants with erythroblastosis. In each case, the sample was taken shortly after admission to the hospital and just prior to an exchange transfusion.

Table VI shows daily bilirubin levels in a number of infants with erythroblastosis who were treated by exchange transfusion. It can be seen that the levels in these infants are much higher than in normal infants and that the average age at which the maximum level is reached is less than two days. There is no doubt that the subsequent course of the bilirubin level is greatly modified by exchange transfusion. Unfortunately, we have almost no data on the daily changes in serum bilirubin in infants with erythroblastosis not treated by exchange transfusion.

Table VII summarizes the raw data given in the previous tables and permits comparison of each group of infants with the others.

TABLE V. SERUM BILIRUBIN DETERMINATIONS IN INFANTS WITH ERYTHROBLASTOSIS BEFORE EXCHANGE TRANSFUSION. IN EACH CASE, THE BLOOD SAMPLE WAS DRAWN IMMEDIATELY PRIOR TO THE EXCHANGE TRANSFUSION

AGE OF BABY (HR.)	NO. OF INFANTS	AVERAGE (MG. %)	MAXIMUM (MG. %)	MINIMUM (MG. %)
0- 6	141	5.77	28.6	0.77
7-12	35	12.40	27.1	2.05
13-18	17	12.50	25.5	4.12
19-24	16	16.70	57.2	5.86
25-36	11	18.80	28.6	8.48
37-48	1	15.10	—	—
49-60	3	33.70	48.6	22.00
61-72	2	30.20	31.3	28.90

DISCUSSION

These studies demonstrate once again that increase of serum bilirubin occurs in the first day or two of life in most babies, though not in all. It is now accepted by most observers that this "normal" increase is at least in part the result of the failure of the infant to dispose of bilirubin during this period. The data confirm the previous reports[20, 23] that physiologic hyperbilirubinemia is not caused by blood group incompatibility, but occurs in full-term babies, and more often in premature babies, irrespective of the blood groups.

The prolonged elevation of bilirubin in premature compatible infants con-

TABLE VI. DAILY TOTAL SERUM BILIRUBIN LEVELS IN INFANTS WITH ERYTHROBLASTOSIS TREATED WITH EXCHANGE TRANSFUSION

	ANTI	GESTATION (WK.)	CORD	1 DA.	2 DA.	3 DA.	4 DA.	5 DA.	AGE AT EXCHANGE TRANSFUSION (HR.)
Stap	D	40	2.5	31.8 (31)	16.6 (44)	15.6 (70)	13.5 (92)	7.9 (115)	7, 31
Laza	D	39		20.3 (20)	25.5 (37)	17.6 (61)	—	16.5 (109)	4, 20
Snyd	D	40	9.1	24.4 (25)	24.4 (49)	17.6 (65)	—	—	1, 25, 49
Ston	A	39	3.9	13.2 (18)	22.7 (44)	17.2 (68)	12.1 (94)	—	44
Adel	D	39	4.5	20.8 (25)	14.6 (44)	6.1 (68)	2.8 (92)	0.7 (117)	2, 25
Carl	A	32	—	19.0 (18)	16.2 (38)	10.0 (62)	5.8 (86)	—	18, 38
Ells	A	35½	—	14.3 (30)	18.0 (47)	18.7 (72)	10.0 (96)	—	33
McGa	D	37	8.3	15.5 (32)	13.2 (55)	10.0 (79)	—	—	1
Stan	D	39	—	14.7 (19)	6.5 (43)	1.4 (69)	—	—	9
Chit	A	39½	3.7	8.5 (25)	11.6 (49)	7.7 (73)	—	—	6
Frai	D	40	4.8	7.5 (20)	10.3 (44)	5.8 (68)	2.9 (92)	—	1
Brom	D	39	2.8	8.0 (17)	6.6 (41)	2.7 (65)	—	—	1
Average bilirubin			5.0	16.5	15.5	10.9			
Average age (hr.)				23	45	68			

Figures in parentheses indicate the age of the infants in hours when samples were drawn.

firms the clinical impression that jaundice occurs more frequently and with greater severity than in full-term infants. This supports Weech's[17, 18] concept that physiological jaundice is primarily a reflection of hepatic immaturity. Although the rate of red cell destruction in the premature infant in the first week of life is not definitely known, it is not thought to be greater than in full-term infants.[26] The prolonged icterus must, therefore, be related to the functional immaturity of the liver in the premature infant as might speculate that the occurrence of kernicterus in premature infants without erythroblastosis reported by Zuelzer[28] and Aidin[29] may have been the result of high serum bilirubin in those infants. If so, exchange transfusion might be used in the prevention of kernicterus in premature infants who develop very high levels of serum bilirubin.

In erythroblastosis, there is added to the normal inability of the infant to dispose of bilirubin an increased rate

TABLE VII. AVERAGE SERUM BILIRUBIN IN VARIOUS GROUPS OF INFANTS, SUMMARIZING DATA IN TABLES II, III, IV, AND VI. VALUES ARE EXPRESSED AS MILLIGRAMS PER 100 C.C. SERUM

	CORD BLOOD	1 DA.	2 DA.	3 DA.	4 DA.	MAXIMUM
12 normal "compatible" infants	2.2	5.7 (23)	7.1 (47)	6.6 (71)	4.9 (95)	7.9 (53)
12 normal "incompatible" infants	2.0	5.7 (22)	6.5 (46)	5.8 (70)	4.5 (94)	7.4 (47)
15 premature infants under 2,250 grams	1.3	5.4 (27)	8.1 (51)	10.7 (75)	11.2 (99)	12.4 (85)
11 premature infants of less than 37 weeks' gestation	1.2	6.7 (26)	9.6 (50)	13.2 (74)	14.2 (98)	15.3 (94)
12 infants with erythroblastosis with exchange transfusion	5.0	16.5 (23)	15.5 (45)	10.9 (68)	—	18.6 (34)

Figures in parentheses represent average age in hours.

demonstrated by Obrinsky[27] with sulfobromophthalein studies. The similarity between the bilirubin levels in premature and mature infants during the first two days suggests that the fundamental mechanism is the same in both groups, but that it persists longer in premature infants. The high levels seen in some premature infants on the third, fourth, and fifth days of life are equal to the levels usually seen in erythroblastosis and exceed what appears to be the minimum safe level with respect to kernicterus.[2, 4] One of blood destruction, and large amounts of bilirubin accumulate. This results in a rapid rise of indirect bilirubin in the serum of such infants and, in many of them, concentrations that are rarely if ever attained in any other clinical condition. The data do not support the commonly held hypothesis that infants with erythroblastosis have at birth functional damage to their livers as a result of the disease process. This group of twelve erythroblastotic babies, who were treated by exchange

transfusion, began to clear their bilirubin at least as quickly as did normal babies without erythroblastosis (Table VII).

It is obvious that the determination of serum bilirubin is of considerable diagnostic value in the neonatal period. Levels above 3 mg. per cent in the cord blood usually mean erythroblastosis, and levels above 6 mg. nearly always do, although levels below 3 mg. per cent do not necessarily rule it out. Levels above 10 mg. per cent in the first twenty-four hours of life are seen in most cases of erythroblastosis, and are seen but rarely in other infants. Serum bilirubin above 10 mg. per cent in the first twenty-four hours is not physiological even in premature infants. The same can be said for definite jaundice of the skin noted during the first twenty-four hours of life. In the treatment of erythroblastosis, measurements of serum bilirubin are of great value since they appear to indicate the prognosis so far as kernicterus is concerned[2, 4] and allow a rational use of exchange transfusion in the prevention of kernicterus.

Four of the twelve cases of erythroblastosis shown in Table VI were caused by maternal antibodies against blood group A in Group A infants. So far as we have been able to determine, serum bilirubin is as valuable in the diagnosis and p r o g n o s i s of erythroblastosis caused by the antibodies anti-A or anti-B as it is in the cases of Rh incompatibility. Actually, it is relatively more valuable at the present time owing to the fact that the serological tests which are so reliable in Rh incompatibility are so difficult to interpret in ABO incompatibility.

SUMMARY

1. Cord bilirubin levels of full-term "compatible," full-term "incompatible," and premature infants are essentially the same. The average cord bilirubin level of infants with erythroblastosis is more than double that of infants without erythroblastosis and a level above 5 mg. per cent is strongly suggestive of this disease.

2. Normal infants usually show a rise of bilirubin during the first day of life, but infants with erythroblastosis show a marked elevation during this period.

3. Normal full-term infants reach their peak elevation of bilirubin at about two days of life, whereas the peak bilirubin of premature infants is attained on the fourth day of life, on the average. The peak elevation of bilirubin of premature infants not only occurs later than that of full-term infants, but reaches higher levels, confirming the clinical impression that physiological jaundice is more severe and more prolonged in the premature infant than in the full-term infant.

4. In this series, infants with erythroblastosis, treated by exchange transfusion, have their bilirubin peak during the second day of life, on the average. Exchange transfusion greatly modifies the bilirubinemia in these infants. A level of serum bilirubin above 10 mg. per cent during the first twenty-four hours of life, or the appearance of skin icterus during this period, must be considered due to erythroblastosis until proved otherwise.

5. Determinations of the level of serum bilirubin during the first two days of life are of great diagnostic value with respect to erythroblastosis, particularly in cases caused by ABO

incompatibility. They are of even greater value as a therapeutic guide in the use of replacement transfusion.

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REFERENCES

1. Mollison, P. L., and Cutbush, M.: Hemolytic Disease of the Newborn: Criteria of Severity, Brit. M. J. **1**: 123, 1949.
2. Mollison, P. L., and Cutbush, M.: A Method of Measuring the Severity of a Series of Cases of Hemolytic Disease of the Newborn, Blood **6**: 777, 1951.
3. Mollison, P. L.: Personal communication.
4. Hsia, D. Y. Y., Allen, F. H., Jr., Gellis, S. S., and Diamond, L. K.: Erythroblastosis Fetalis. VIII. Studies of Serum Bilirubin in Relation to Kernicterus, New England J. Med. **247**: 668, 1952.
5. Goldbloom, A., and Gottlieb, R.: Icterus Neonatorum, Am. J. Dis. Child. **38**: 57, 1929.
6. Mitchell, J. M.: Relationship of Jaundice and Weight to Blood Values in the Newborn Infant, Am. J. Dis. Child. **38**: 518, 1929.
7. Book, N.: Icterus Neonatorum, Canad. M. A. J. **33**: 269, 1935.
8. Martin, L. C., and Evans, S. M.: Blood Counts of Newborn Infants in Relation to Icterus Neonatorum, Arch. Dis. Child. **10**: 355, 1935.
9. Bonar, B. B.: The Icterus Index in the Newborn Infant, Am. J. Dis. Child. **50**: 1143, 1935.
10. Snelling, C. E.: Icterus Neonatorum, J. PEDIAT. **2**: 399, 1933.
11. Weiner, S. B., and Reiner, M.: Icterus Index in the Newborn, Proc. Soc. Exper. Biol. & Med. **41**: 83, 1939.
12. Reiner, M., and Weiner, S. B.: Jaundice in Infants and Children, Am. J. Dis. Child. **61**: 752, 1941.
13. Schick, N., Weiner, S. B., and Reiner, M.: Icterus Index of Cord Blood, Am. J. Dis. Child. **64**: 655, 1942.
14. Mollison, P. L.: Physiological Jaundice of the Newborn, Lancet **1**: 513, 1948.
15. Ross, S. G., Waugh, T. R., and Malloy, H.: The Metabolism and Excretion of Bile Pigment in Icterus Neonatorum, J. PEDIAT. **11**: 397, 1937.
16. Waugh, T. R., Merchant, F. T., and Maughan, G. B.: Direct and Total Bilirubin Determinations Over a 9-Day Period on the Newborn, Am. J. M. Sc. **199**: 9, 1940.
17. Davidson, L. T., Merritt, K. K., and Weech, A. A.: Hyperbilirubinemia in the Newborn, Am. J. Dis. Child. **61**: 958, 1941.
18. Weech, A. A.: Genesis of Physiological Hyperbilirubinemia, Advances in Pediatrics **2**: 346, 1947.
19. Findlay, L., Higgins, G., and Stanier, M. W.: Icterus Neonatorum; Incidence and Cause, Arch. Dis. Childhood **22**: 65, 1947.
20. Fashena, G. J.: Mechanism of Hyperbilirubinemia in the Newborn Infant, Am. J. Dis. Child. **76**: 196, 1948.
21. Halbrecht, I., and Brzoza, H.: Evaluation of Hepatic Function in Newborn Infants by Means of Chemical Study of Cord Blood, Am. J. Dis. Child. **79**: 988, 1950.
22. Smith, C. A.: The Physiology of the Newborn Infant, Springfield, Ill., 1951; Charles C Thomas, p. 149.
23. Wexler, L. B., and Wiener, A. S.: Blood Group Factors and Physiological Icterus, Brit. M. J. **1**: 1228, 1951.
24. Halbrecht, I.: Icterus Precox, J. PEDIAT. **39**: 185, 1951.
25. Hsia, D. Y. Y., Hsia, H. H., and Gellis, S. S.: A Micromethod for Serum Bilirubin, J. Lab. & Clin. Med. **40**: 610, 1952.
26. Blackfan, K. D., and Diamond, L. K.: Atlas of the Blood in Children, New York, 1944, The Commonwealth Fund, p. 25.
27. Obrinsky, W., Donley, M. L., and Brauer, R. W.: Sulfobromophthalein Sodium Dye Excretion Test, Pediatrics **9**: 421, 1952.
28. Zuelzer, W. W., and Mudgett, R. T.: Kernicterus: Etiologic Study Based on an Analysis of 55 Cases, Pediatrics **6**: 452, 1950.
29. Aidin, R.: Neonatal Death, With Special Reference to Sixth Day Disease, Med. Press **226**: 88, 1951.

PARATHION POISONING IN CHILDREN

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AT LEAST ten deaths have been reported in this country arising from the careless handling of the organic phosphate insecticide, parathion.[3, 4, 6, 9] These deaths have occurred in adults engaged either in the manufacture of the chemical or in its use in the field for agricultural purposes. (An excellent review of the subject is found in a report by the Council on Pharmacy and Chemistry in the *Journal of the American Medical Association*.[5]) It is the purpose of this paper to present the case history of an accidental death of a child due to parathion. Other instances of poisoning in children also are presented.

HISTORY

During World War II, German scientists engaged in a search to find a substitute for nicotine which was unavailable to them because of war. These scientists developed an organic phosphate which they named "Bladan" and which proved to be more efficient than the nicotine alkaloid in controlling aphids, mites, and other insect pests. American research chemists discovered that the active ingredient in the German product was tetraethyl pyrophosphate, $(C_2H_5O)_4P_2O_3$. The formula for parathion was discovered in the I. G. Farbenindustrie files by British and American intelligence teams after the war. The chemical was first manufactured for commercial use in this country in 1948,[1] having received extensive field study during the preceding year.

From the Communicable Disease Center, Public Health Service, Federal Security Agency.

THE AGRICULTURAL USE OF PARATHION

Parathion is a multipurpose insecticide accepted for labeling by the United States Department of Agriculture for use against many insects which damage crops. It is used in areas where the following crops are grown: fruit, vegetables, cotton, tobacco, alfalfa, cereal grains, hops, nuts, berries, and in many areas it is used to control insects on ornamental plants. The use of this insecticide is widespread.

Because of the extreme toxicity of parathion, it is not available for use in its pure technical form. It is commercially available as a 25 per cent emulsion or water-wettable powder or dust. The farmer or commercial applicator reduces the 25 per cent material to a formulation usually varying from 0.001 to 5 per cent by adding water or inert materials such as clay. The final strength of the material applied depends upon the method of application and the insect the farmer is trying to control.

THE CHEMISTRY OF PARATHION

Technical parathion contains 95 per cent or more of the pure chemical, 0,0-diethyl-0-*p*-nitrophenyl thiophosphate. The chemical is an ester of thiophosphoric acid, having the empirical formula $C_{10}H_{14}NO_5PS$. This compound is only slightly soluble in water, but is completely miscible in

organic solvents such as alcohol, ethers, and animal and vegetable oils. It is stable to hydrolysis in water and in acid solutions.

TOXICOLOGY OF THE ORGANIC PHOSPHATES

The toxicity of the organic phosphates can best be explained by their destruction of the cholinesterase enzymes of the nervous system, and, incidentally, of other tissues, thereby allowing the nervous tissue to accumulate an excess of acetylcholine. According to the most accepted theory, acetylcholine is the actual mediator of nerve impulses at pre- and postganglionic parasympathetic endings, at the preganglionic sympathetic endings, at a few postganglionic sympathetic endings (sweat glands, uterus, certain vasodilators), at the myoneural junction, and perhaps in parts of the central nervous system.[2] An excess of acetylcholine (either as a result of injection or as the result of accumulation caused by a deficiency of cholinesterase) causes the same effects as may be seen following stimulation of parasympathetic nerves.

It has been estimated from results obtained in animal experimentation than the lethal oral dose of technical parathion in a man weighing 70 kilograms would be in the range of 12 to 20 mg. The acute oral toxicity of parathion is approximately 70 times that of DDT.

The organic phosphates are readily absorbed through the skin, the conjunctiva, and the respiratory and the gastrointestinal tracts.

SIGNS AND SYMPTOMS SEEN IN ORGANIC PHOSPHATE POISONED INDIVIDUALS

For descriptive purposes, the symptoms of organic phosphate insecticide poisoning may be conveniently classified, depending on whether they resemble the symptoms caused by the drug muscarine, symptoms caused by the drug nicotine, or symptoms caused by a general dysfunction of the central nervous system. During the early phases of intoxication, the muscarinic symptoms are manifest. In more severe poisoning, all the signs and symptoms may be observed.

I. Muscarinic
   - A. Gastrointestinal: anorexia, nausea, vomiting, abdominal cramps, diarrhea, tenesmus, substernal pressure suggestive of cardiospasm.
   - B. Glands
     1. Sweat glands: increased sweating to profuse diaphoresis.
     2. Salivary glands: increased salivation.
     3. Lacrimal glands: increased lacrimation.
   - C. Heart and Peripheral Vascular System: increased blood pressure, increased pulse rate, palpitation, flushing of the skin.
   - D. Respiratory System: bronchospasm giving "tightness of the chest," asthmatic-like breathing, increased bronchial secretions.
   - E. Pupils: myosis, pin-point pupils, dimness of vision.
   - F. Ciliary Body: blurring of vision.
   - G. Bladder: frequency, involuntary micturition.

II. Nicotinic
   - A. Muscles
     1. Muscular fasciculations, especially of the eyelids.
     2. Muscle cramps, especially of the legs.
     3. Weakness.
     4. Muscular incoordination.

III. Central Nervous System
   - A. Restlessness, anxiety, giddiness, drowsiness.
   - B. Headache: severe and not relieved by analgesics.
   - C. Slurred speech.
   - D. Mental confusion.
   - E. Visual distortions.
   - F. Convulsions.
   - G. Coma.

TREATMENT OF ORGANIC PHOSPHATE POISONING

These patients are medical emergencies. The clothes should all be removed and the patient thoroughly scrubbed with soap and water. Gastric lavage should be done if there is suspicion that the patient swallowed the poison. Atropine is the best antidote available. Keep the patient fully atropinized if symptoms appear. These poisoned patients can tolerate more atropine than the normal person. Never give morphine. If pulmonary secretions have accumulated, a suction apparatus as well as a tracheotomy set should be available. In patients with severe respiratory symptoms, the regime used for patients with bulbar poliomyelitis may be indicated. Complete recovery may be obtained even after many hours of artificial respiration have been necessary. Medication must be continued during the entire emergency which may last as long as twenty-four to forty-eight hours.

The diagnosis of organic phosphate poisoning rests upon the history of exposure, the symptoms exhibited, and the chemical determination of the enzyme cholinesterase.

THE CHOLINESTERASE TEST

The cholinesterase activity of the red blood cells and the plasma can be determined. The analytical procedure depends upon a quantitative measurement of the acid produced by the action of cholinesterase on acetylcholine. The acid production can most conveniently be measured according to the method of Michel.[7] According to this system, the cholinesterase value is expressed as a change in pH units per hour of a buffered solution under specified conditions.

The plasma cholinesterase of normal adults may vary from 0.4 to 1.6 units, and the red blood cell values may vary from 0.4 to 1.0 unit in the nonexposed individual. The average red blood cell cholinesterase level observed in groups tested to find a mean has been found by various investigators to be in the neighborhood of 0.7 unit, and the plasma cholinesterase to be slightly higher, 0.8 to 0.9 unit. The plasma cholinesterase in the nonexposed individual usually is higher than the red blood cell value. A cholinesterase level below 0.5 unit in the red blood cells or plasma fraction is highly suggestive of organic phosphate intoxication in an exposed individual. A cholinesterase level below 0.3 unit in either the red blood cells or plasma is probably diagnostic of organic phosphate intoxication provided the patient has not been taking other cholinesterase-inhibiting drugs, such as eserine or prostigmine, or does not have a liver disease which could lower the cholinesterase production.[8]

The test is exceedingly useful in following a case of organic phosphate poisoning. The plasma cholinesterase recovers more rapidly following poisoning than the red blood cell cholinesterase. The red blood cell cholinesterase usually returns to a normal in from six weeks to two months.

Most clinical laboratories are not equipped to do the cholinesterase test. The United States Public Health Service laboratories in Wenatchee, Wash. (Post Office Box 73), and at Savannah, Ga. (Post Office Box 769) are experienced with the procedure. A list of other laboratories able to do the test has been compiled by the American Cyanamid Company (30 Rockefeller Plaza, New York, N. Y.). The different laboratories prefer samples pre-

pared in slightly different ways, and any interested person should make specific inquiry to the laboratory of his choice. However, in emergency, any laboratory should be able to make a useful test on 3 c.c. of oxalated, citrated, or better, heparinized blood shipped under refrigeration by the fastest route.

CASE HISTORIES

CASE 1.—L. D. N., a 9-month-old white female infant, just prior to noon of Sept. 21, 1951, while playing in her yard, discovered a can containing a pasty mixture of parathion and DDT which her father had discarded approximately one week previously. (Chemical analysis of this paste after a quantity of its water had evaporated showed it contained 38 per cent parathion; the DDT content was not determined.) The infant played with the can and undoubtedly transmitted some of the paste into her mouth. After the parents discovered her, she was bathed, her mouth was washed out, and she was put to bed. She slept restlessly for about one hour, then awoke screaming and shivering. In view of these symptoms and recalling the exposure to parathion and DDT, the parents called the family physician who advised that the child be taken to the hospital where she was admitted at 5:30 P.M., Sept. 21, 1951.

The nurse reported that the patient was restless, irritable, and crying when she was admitted to the emergency room. A stomach lavage was done immediately and 1/300 grain of atropine was administered hypodermically. At 5:45 P.M. the infant was removed to the children's ward, at which time the pulse rate was 128 per minute and the temperature was 99.4° F. She was next given a soapsuds enema and one dram of milk of magnesia. She was then given elixir of phenobarbital to stop her violent crying. By 7:30 P.M. a considerable amount of mucus was forming in the bronchi, and nasal suction was used followed by a second dose of 1/150 grain of atropine. The cyanosis deepened and respiration became very shallow. The patient became comatose. Artificial respiration and oxygen were started, but at 8:00 P.M., ten minutes after respiratory failure, cardiac action stopped. One-third cubic centimeter Adrenalin injected into the heart had no effect. No cholinesterase test was done.

CASE 2.—C. W., a 2½-year-old white boy, on Oct. 10, 1951, while playing with his sister, found four sacks which contained a 25 per cent water-wettable powder parathion. The sister was found dumping the powder over the boy's head. It was estimated that the two children were in contact with the material for at least one-half hour. There was no evidence on discovery that the boy had taken any of the powder into his mouth. About one-half hour after the children were discovered, the boy began to vomit. The mother, who was cognizant of the extreme danger of this material, telephoned her pediatrician who advised immediate hospitalization. On the way to the hospital the boy vomited again. He was admitted to the clinic and atropinized there. He was then transferred to the hospital for observation. Physical examination of the child was entirely negative except for tachycardia. He was discharged from the hospital the following day, about thirty-one hours after his exposure to parathion began. Blood cholinesterase values are given in Table I.

CASE 3.—S. W., a 5-year-old white girl, is the sister of the boy in Case 2. This girl had no symptoms but was hospitalized for observation and was atropinized. The physical examination of the girl was negative. She was discharged with her brother. Blood cholinesterase values are given in Table I.

CASES 4 and 5.—D. D. and R. D.: Case 4 is a 23-month-old white male and Case 5 is a 3-year-old white male, the brother of Case 4. D. D. was seriously poisoned while R. D., was not poisoned. This discussion concerns D. D. specifically and R. D. only in passing.

D. D. a 23-month-old white male, after his lunch on Sept. 9, 1952, while playing with his brother, aged 3 years, discovered a can of parathion (25 per cent liquid emulsion) in the basement of their home. The older child opened the can and the two of them started dumping dirt into it. After but a short time, they were discovered by their mother who immediately washed them off and put them to bed for their naps. This was approximately 2:00 P.M. The mother states that she was not sure whether they had contaminated their skin with the insecticide.

After an hour, the youngest, D. D., awakened exhibiting the following symptoms: myosis, wheezing, and his eyes "appeared to be glassy." The family doctor was called and advised immediate hospitalization. They arrived at the clinic at approximately 4:00 P.M., and the younger was given 1/150 grain of atropine and transferred to the hospital. A gastric lavage was immediately done. By this time the boy was exhibiting both the muscarinic symptoms previously mentioned and moist râles in his chest, as well as the nicotinic symptoms, muscular twitching, tremors, and muscular incoordination.

By 5:00 P.M. the boy was atropinized and the muscarinic symptoms had disappeared. On physical examination his eyes were dilated, his chest was clear and his face was well flushed. The nicotinic symptoms remained.

Blood was drawn on admission for the cholinesterase test. At 7:30 P.M. the results were reported; red blood cell cholinesterase 0.05 unit and plasma 0.09 unit. His brother, who exhibited no symptoms, was also sampled and his results at the same time were: red blood cells 0.65 unit and plasma 1.15 unit. He was not admitted for observation because his cholinesterase test ruled out the possibility of serious poisoning.

The younger boy was treated with atropine as follows: 1/300 grain every four hours during the first twenty-four hours and then discontinued, to be restarted only if he redeveloped his muscarinic symptoms. Twenty-four hours after exposure he was asymptomatic and remained so. A blood test run for cholinesterase taken twenty-four hours after poisoning showed a red blood cell cholinesterase value of 0.19 unit and plasma value of 0.26 unit. He was discharged from the hospital the following noon, Sept. 11, 1952.

TABLE I. SUMMARY OF THE FIVE CASES SHOWING EXPOSURE, SYMPTOM DEGREE, AND BLOOD CHOLINESTERASE LEVEL

CASE	EXPOSURE	PARATHION FORMULATION	SYMPTOMS	CHOLINESTERASE VALUES			
				DATE	HOUR	Δ PH HR. R.B.C.	Δ PH HR. PLASMA
1. L. D. N.	Probable oral Known dermal	38% paste	Fatal	------	----	----	----
2. C. W.	Doubtful oral Known dermal	25% dust	Moderate	10/10/51 10/11/51 1/16/52	12:00 15:00 11:00	0.18 0.28 0.51	0.12 0.23 0.72
3. S. W.	Doubtful oral Known dermal	25% dust	None	10/10/51 1/16/52	12:00 11:00	0.59 0.57	0.83 0.93
4. D. D.	Doubtful oral Known dermal	25% liquid emulsion	Severe	9/ 9/52 9/16/52	19:30 19:20	0.05 0.19	0.09 0.26
5. R. D.	Doubtful oral Doubtful dermal	25% liquid emulsion	None	9/ 9/52	19:30	0.65	1.15

DISCUSSION

The case histories of five children have been presented, each with a known exposure to the organic phosphate, parathion.

In Case 1 it was not possible to obtain blood for the cholinesterase test. Studies on adults with severe parathion poisoning exhibiting comparable symptomatology have shown almost a total loss of blood cholinesterase activity. Case 4, with symptoms not as

severe, showed an almost total loss of the enzyme. This child received an overwhelming dose of parathion with known dermal exposure as well as probable oral exposure.

Case 2 had an intermediary exposure. The cholinesterase activity in this boy was markedly depressed. His exposure was most likely exclusively dermal.

Case 3 had less exposure with absorption of the poison through the skin of her hands and forearms only. She showed a slight depression of her plasma cholinesterase activity.

Case 4 exhibited both the muscarinic and nicotinic symptoms of parathion poisoning. The atropine controlled the former and failed to control the latter. Although the mother did not know whether the skin of the boys was contaminated with the parathion emulsion, the cholinesterase test in the younger child clearly established the diagnosis of severe organic phosphorus insecticide poisoning and ruled out serious poisoning in the older boy. The second test drawn twenty-four hours following exposure showed a marked regeneration of the enzyme in the younger patient. Prompt treatment with atropine probably saved the child's life.

Case 5 may have had only a very slight exposure and he showed no symptoms. The cases are summarized in Table I.

It should be noted that the strength of the parathion to which these children were exposed was far greater than that of formulations actually applied to crops.

It must be pointed out that these accidents were due to gross carelessness. The parents of these children, after living for years in agricultural areas, have become accustomed to the "poison" label and, apparently, familiarity has bred contempt. The organic phosphate chemicals demand the respect of the clinician as well as the farmer. Again, the best cure of poison accidents is their prevention.

SUMMARY

1. Cases of parathion poisoning in children have been presented; one, a fatality.

2. These accidents were due to gross carelessness on the part of their parents.

3. Specific treatment is available and may be lifesaving if properly administered.

REFERENCES

1. Anonymous: Parathion Offered by American Cyanamid, Chem. & Eng. News 26: 118, 1948.
2. Best, C. H., and Taylor, N. B.: Physiological Basis of Medical Practice, ed. 4, Baltimore, 1945, Williams & Wilkins Co., p. 946.
3. Grob, D., Garlick, W. L., and Harvey, A. M.: The Toxic Effects in Man of the Anticholinesterase Insecticide Parathion (p-Nitrophenyl Diethyl Thionophosphate), Bull. Johns Hopkins Hosp. 87: 106, 1950.
4. Grob, D., Garlick, W. L., Merrill, G. G., and Freimuth, H. C.: Death Due to Parathion, an Anticholinesterase Insecticide, Ann. Int. Med. 31: 899, 1949.
5. Haller, H. L., Rohwer, S. A., DuBois, K. P., Grob, D., Abrams, H. K., Hamblin, D. O., Marchand, J. F., Lehman, A. J., Hartzell, A., and Ward, J. C.: Pharmacology and Toxicology of Certain Organic Phosphorus Insecticides, J. A. M. A. 144: 104, 1950.
6. Hamblin, D. O., and Marchand, J. F.: Parathion Poisoning, Am. Pract. & Digest Treat. 2: 1, 1951.
7. Michel, H. O.: An Electrometric Method for the Determination of Red Blood Cell and Plasma Cholinesterase Activity, J. Lab. & Clin. Med. 34: 1564, 1949.
8. Vorhaus, L. J., Scudamore, H. H., Cabuzda, C. J., Morey, C. R., Maloney, M. A., and Kark, R. M.: Serial Serum Cholinesterase Determinations in Liver Disease, J. Lab. & Clin. Med. 33: 1475, 1948.
9. Williams, J. W., and Griffiths, J. T., Jr.: Parathion Poisoning in Citrus Spray Operations, Florida M. A. J. 37: 681, 1951.

AN EVALUATION OF BENEMID P-(DI-N-PROPYLSULFAMYL)-BENZOID ACID

DOSAGE SCHEDULE IN CHILDREN

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WITH TECHNICAL ASSISTANCE OF CAROLYN AXNER

IT HAS been shown[1, 2, 3, 4] that a new derivative of benzoic acid, Benemid,* p-(di-n-propylsulfamyl)-benzoic acid, effectively blocks the renal tubular transport mechanism for penicillin, phenosulfonphthalein, para-aminohippurate, and para-aminosalicylic acid. It also increases the excretion of uric acid and lowers the uric acid blood level.[5, 6] No toxicity was demonstrated by months of daily medication in dogs and the kidney tubular blocking effects were completely reversible upon discontinuing the Benemid.

In man, Boger and associates[7] have shown that a dose of 2 Gm. a day in adults may be continued for as long as nine months without evidence of renal toxicity. Benemid has all the pharmacologic actions of carinamide. However, it does not have the drawbacks of the latter drug, namely, the large amount required—up to 24 Gm. per day in the adult, which has to be given in divided doses every four hours, fairly frequent gastric distress on full dosage, ability to induce sensitivity as manifest by cutaneous rashes, and excretion as a sodium salt which removes considerable amounts of sodium from the body.[8]

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The expenses of this study were borne by a grant-in-aid from Sharp & Dohme, Inc.

*Sharp and Dohme's trademark for this drug which has been given the generic designation "probenecid."

Benemid is a cheap, simple synthetic derivative of benzoic acid (Fig. 1) which is extremely stable, sparingly soluble in water, and almost tasteless. It is readily absorbed when given by mouth and Boger and associates[7] found that within two to four hours the plasma concentrations matched those following intravenous administration of the same dose of Benemid.

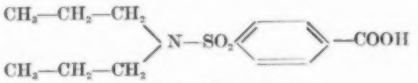

Fig. 1.—Benemid.

Benemid does not appear in the urine and the exact mode of elimination from the body is not known. Plasma levels fall somewhat more slowly than those of mannitol so presumably it is excreted only by glomerular filtration and reabsorbed by the renal tubules. Since Benemid is not excreted by the renal tubules, its blocking of tubular transport of penicillin cannot be explained as simple competition for the same transport mechanism.

The action is specific. In the presence of Benemid when tubular secretion of penicillin and PSP are inhibited, the secretion of N-methyl-nicotinamide continues. Also, while the reabsorption of both phosphate and uric acid is inhibited, the reabsorption of neither glucose nor arginine[7] is af-

fected. The mode of action is, therefore, not a nonspecific toxic effect on the tubule.

Benemid seems destined for considerable clinical application where prolonged or very high penicillin blood levels are desired. The purpose of the research reported here was to determine the optimal dose of Benemid for children.

METHODS

Afebrile convalescent or normal patients, aged 2 months to 12 years with normal renal function, were selected. Crystalline penicillin G was given intramuscularly in single doses of 10,000 units per kilogram of body weight. Capillary blood was drawn[9] for penicillin levels at intervals of one-half, one, three, and five hours, or at one, two, and three hours after administration. After an interval of one to four days the same patient received the same dose of intramuscular penicillin two hours after an oral dose of Benemid. Blood was drawn for penicillin levels as before. The serum penicillin concentrations expressed in units per milliliter of serum were plotted on semilogarithmic paper. The excretion rates for the patients with penicillin alone, and penicillin with Benemid, were computed as constants (K_1 and K_2, respectively), and compared with the constant of excretion rate calculated theoretically for glomerular excretion alone (K_3).[10] From these values it was possible to calculate the percentage of suppression of tubular excretion caused by any given dose of Benemid.

Penicillin was assayed by the micromethod described by Hildick-Smith[9] with *Staphylococcus aureus* (F.D.A. strain 9801) as the test organism. Benemid plasma levels were determined by the methylene blue technique of Tillson and her colleagues.[11]

RESULTS

Sixteen children received forty-eight injections of the standard dose of penicillin either alone or together with single doses of Benemid of varying size. When the serum concentrations of penicillin were plotted as just described, a progressive delay in the excretion of penicillin occurred with each increment in the dosage of Benemid up to a certain maximum. A sample of the observations and calculations on one patient are shown (Table I and Fig. 2). The minimal dose of Benemid causing maximal decrease of excretion rate was taken as the dose causing complete suppression of tubular function. In these tests it was not deemed necessary to assay for penicillin until it disappeared from the serum. Once the penicillin is equilibrated in the body fluids the serum level falls at a constant rate as shown by Eagle and Newman.[12] If it is desired, the duration of effective serum level can be approximated by extending the slope to the base line (see Fig. 2).

TABLE I. PATIENT J. M.

MG. BENEMID PER KG. BODY WEIGHT	CONSTANTS OF EXCRETION RATE	PER CENT TUBULAR SUPPRESSION
0	3.0 (K_1)	0
14	1.14 (K_2)	88
27	.86 (K_2)	102
41	.70 (K_2)	105
Estimate complete suppression	.91 (K_3)	100

Fig. 3 is a graphic summary of the percentage of tubular suppression produced by various single doses of Benemid in these sixteen children. A dose of approximately 15 mg. per kilo-

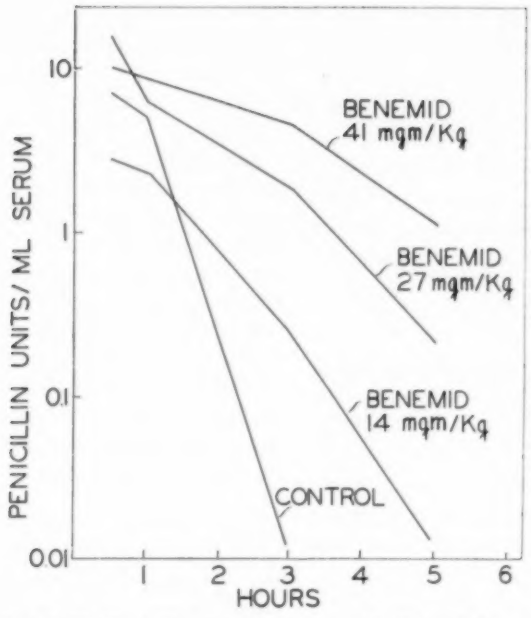

Fig. 2.—Patient J. M. Penicillin excretion curves with different doses of Benemid. Penicillin 10,000 units per kilogram of body weight intramuscularly with the amounts of Benemid shown.

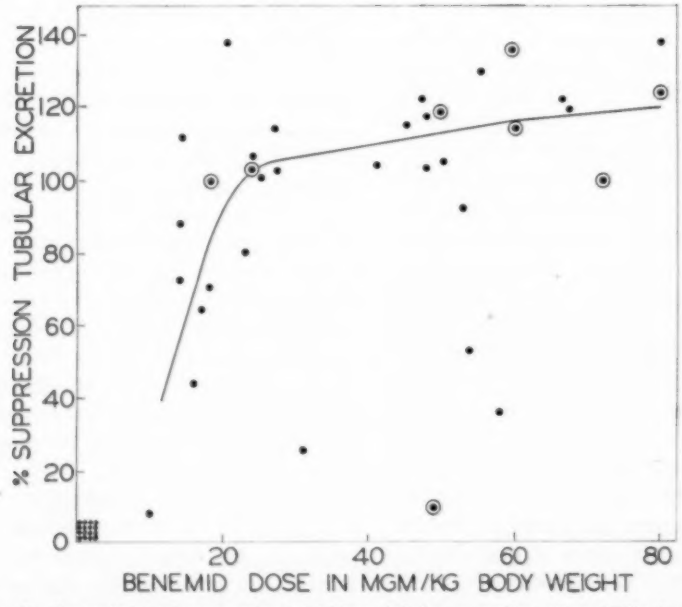

Fig. 3.—Percentage of suppression of kidney tubular excretion of penicillin in sixteen children who received single intramuscular doses of penicillin together with varying oral doses of Benemid. The circled points indicate levels obtained in infants under 3 months of age.

gram of body weight caused 44 to 110 per cent suppression, 25 mg. per kilogram produced complete suppression, and larger doses in most instances caused slightly greater than calculated 100 per cent suppression of tubular function. The circled points represent infants under 3 months of age and the figures obtained for them do not differ from those that are obtained in the older children. Three abnormally low values were obtained on doses of Benemid greater than 30 mg. per kilogram.

In order to approximate the optimal single dose of Benemid more closely, nine patients were given 10 mg. of Benemid per kilogram of body weight and another nine patients were given 60 mg. per kilogram of body weight along with the standard dose of penicillin. Of those receiving the smaller dose of Benemid, three showed normal clearance of penicillin, two showed flat curves approaching those of glomerular filtration alone, and the remainder fell between with an average for the nine children of about 40 per cent tubular suppression. All nine children who received a 60 mg. dose of Benemid showed flat curves consistent with complete suppression of renal tubular secretion of penicillin. Fig. 4 summarizes the average penicillin slope of each group of nine children.

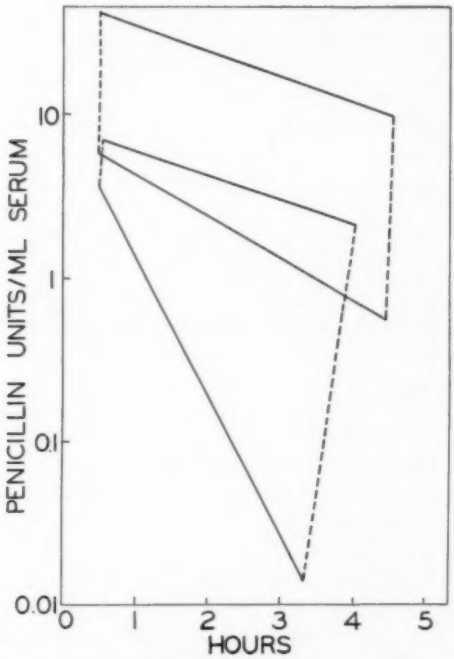

Fig. 4.—Penicillin excretion curves in two groups of nine children who received, respectively, 10 or 60 mg. per kilogram of body weight of Benemid two hours before intramuscular penicillin in a dose of 10,000 units per kilogram of body weight. The upper box contains all the curves of the nine patients who received 60 mg. of Benemid, and the lower box, all the curves of those who received 10 mg. of Benemid.

While a single dose of 10 mg. per kilogram of body weight was suboptimal in many children, it was ob-

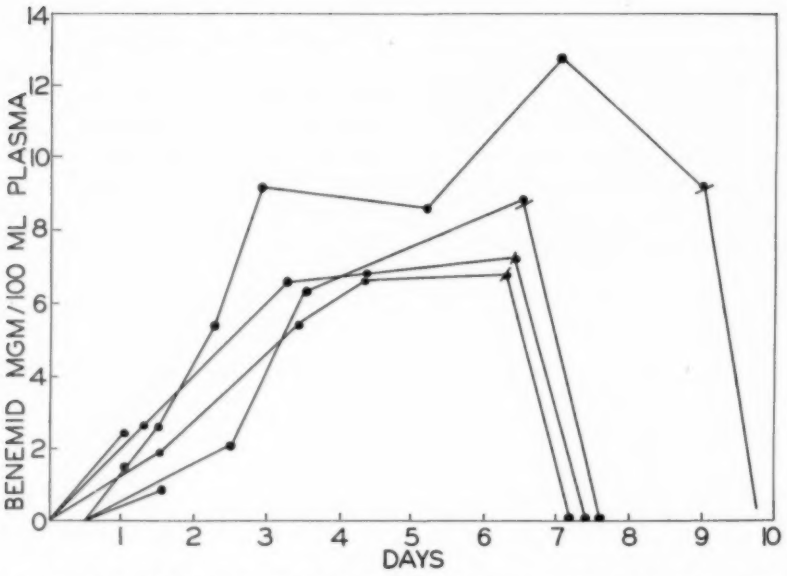

Fig. 5.—Benemid plasma levels in six children who received 10 mg. per kilogram of body weight every six hours. The cross bars after sixth day indicate the last dose of Benemid. Plasma levels build up slowly in this dosage.

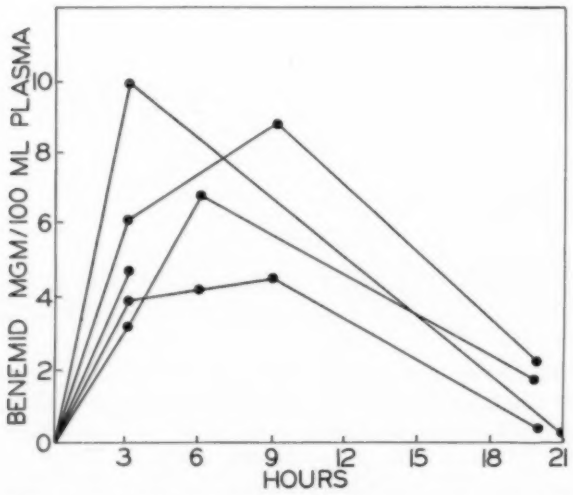

Fig. 6.—Benemid plasma levels in five children following a single oral dose of 25 mg. per kilogram of body weight.

served that children placed on repeated doses of 10 mg. per kilogram of body weight every six hours showed complete suppression of tubular secretion of penicillin when tested after two days. The slow excretion of Benemid might permit cumulative effects so that the smaller dose when repeated would be adequate. When tested this proved to be the case. In Fig. 5 are shown the Benemid plasma levels on six children who received 10 mg. per kilogram of body weight every six hours. Benemid levels taken four hours after the last dose were determined over a period of several days. These show that on this dosage the plasma concentration increased very slowly. At the end of twenty-four hours four were below 2 mg. per 100 ml. and all were below 2.5 mg. per 100 ml. On the third day all those tested had Benemid levels above 5.0 mg. per 100 ml. and on successive days remained between 6 and 13 mg. per 100 ml. Benemid could not be detected in the plasma within twenty-four hours of discontinuing the dose. Boger and co-workers[7] have shown in adults that plasma levels of 2 to 10 mg. per 100 ml. give significant pharmacologic effects and that levels of over 35 mg. per 100 ml. may lead to nausea in some patients. In children a dose of 10 mg. per kilogram repeated every six hours appears to strike a good balance between absorption and excretion and to maintain a pharmacologic blood level. However, a larger initial loading dose to establish the desired blood concentration quickly would be desirable. By inspection of Fig. 3 it becomes apparent that a single dose of 25 mg. per kilogram of body weight was the least amount which caused complete tubular suppression in all but an occasional patient. This amount of Benemid was given to five children as a single dose and blood levels were determined at intervals of three, six, nine, and twenty hours. As shown in Fig. 6, all these children had Benemid plasma levels above 3 mg. per 100 ml. within three hours. Twenty to twenty-one hours later the levels varied between 0.3 and 2.3 mg. per 100 ml.

As a result of these studies the dosage of Benemid for children below 50 kilograms in weight would appear to be 25 mg. per kilogram of body weight as an initial dose followed by doses of 10 mg. per kilogram of body weight every six hours. For children above this weight the adult standards recommended by Boger and associates[7] can be used. In the clinical and laboratory experience obtained in treating twenty children, this regimen has proved practical and effective in maintaining adequate and yet avoiding excessively high levels.

Among eighty-five children treated with Benemid, three instances of vomiting have been observed. In none of the children was it necessary either to decrease the dose or discontinue the drug and vomiting did not persist. In one patient convalescing from scarlet fever a transient erythematous rash was noted. This eruption faded rapidly on stopping the Benemid and did not recur when Benemid was given again one week later. No other evidences of toxicity were observed even though ten patients received large doses of Benemid (60 mg. per kilogram) every six hours for two weeks. This was six times the dose later found to be optimal. Urinalyses and blood counts in these patients remained within normal limits. Because of the extensive and negative toxicity studies

reported by others,[3] we did not carry out additional studies for toxicity. It can be expected that any substance administered to a large group of people may result in a certain number of allergic manifestations. However, experience in man so far indicates that Benemid has no direct toxicity and a very low allergenic potential.

CLINICAL APPLICATIONS

The greatest single indication for Benemid is the presence of an infection caused by an organism which is relatively resistant to all antibiotics, including penicillin, yet susceptible to a greater penicillin concentration than can be obtained by ordinary dosages. Without increasing the size or frequency of penicillin dosage an average fivefold increase in blood level can be expected when Benemid is given. In one case of staphylococcus osteomyelitis in a 2-year-old child the organism was highly resistant to all antibiotics. It was resistant to 100 units of penicillin but susceptible to 200 units. By placing the child on oral Benemid and 1,000,000 units of intramuscular penicillin every three hours the blood level was maintained above 200 units per milliliter for two weeks and the child recovered. In a similar case, the penicillin level was maintained above 50 units per milliliter until recovery from the infection. Two patients with typhoid fever have been successfully treated with penicillin and Benemid. In one case the organism was resistant to 10 units per milliliter and in the other to 40 units per milliliter. No positive stool cultures were observed after treatment in these two cases. A third patient with typhoid fever made a good clinical response to Chloromycetin but had a persistently positive stool culture for three weeks while receiving large doses of Chloromycetin. The organism was resistant to 25 units of penicillin, sensitive to 50 units. The patient was placed on oral Benemid and given 1 to 2 million units of penicillin per hour by intravenous drip for six hours on each of eight days. Weekly stool cultures remained negative for *S. typhi* for thirty days thereafter. Penicillin blood levels varied between 350 and 27 units per milliliter during the six-hour period on four days when repeated blood levels were determined. On another occasion, a moribund infant of 10 months with meningococcic meningitis and bilateral panophthalmitis, hypopyon, opaque vitreous, and steamy cornea was given Benemid and 1,000,000 units of intravenous penicillin and made a complete recovery. She was also given cortisone during the second week in an effort to delay fibrosis, synechia, and organization of any thrombosed retinal vessels. Ophthalmoscopic examination of the fundus and gross vision were normal on discharge. We have not had an opportunity to treat subacute bacterial endocarditis with Benemid and penicillin but others have reported success by the use of the two drugs in combination.[13] It seems therefore as if Benemid may be indicated in conditions where a very high plasma concentration of penicillin is necessary to favor diffusion into the infected area, or in infections caused by an organism which is resistant to all antibiotics except to penicillin in relatively high concentration.

A combination of Benemid with other forms of penicillin may be indicated under certain circumstances. When Benemid is given with procaine penicillin in infants, the blood level of

penicillin is about doubled, but this is probably of no practical importance. Of more significance might be the combination of Benemid and penicillin in a tablet for oral administration. Recent studies have shown that most acute infections for which penicillin is used can be adequately controlled with oral penicillin. On a standard oral dose per pound of crystalline penicillin the blood levels vary considerably and

TABLE II. PENICILLIN LEVELS FOLLOWING ORAL PENICILLIN-BENEMID TABLET

PATIENT	AGE (YR.)	PENICILLIN UNITS PER POUND	UNITS PENICILLIN PER ML. SERUM: HOURS AFTER DOSE 1	2	3
E. S.	4	2,800 q.6h.	.53		
A. W.	13 mo.	3,000 once	.31	.17	.057
H. L.	3	3,000 once	.255	.32	.143
M. R.	18 mo.	3,000 q.8h.	.84		
E. H.	7	3,000 q.8h.	.61	.27	.196
R. C.	13	3,000 q.8h.	.77	.45	.40
C. B.	13	3,000 q.8h.	.31	.41	.248
P. K.	3	3,000 q.8h.	.44	.38	.245
			.45	.064	.039
T. F.	5	3,135 q.6h.	.37		
			.025		
R. C.	3½	3,125 q.6h.	.46	.37	.14
B. G.	7	3,333 q.6h.	.385	.32	.14
L. W.	6	3,400 q.6h.	1.14	.75	.52
B. K.	3	3,500 q.6h.	.61	.61	.27
D. B.	2	4,000 q.6h.		1.04	.51
M. H.	15 mo.	4,000 q.6h.	1.42	.82	1.32
H. N.	9	4,400 q.8h.		.76	
M. E.	5	5,000 q.8h.	.56	.525	.277
V. C.	4	5,000 q.6h.	.33	.5	
				.25	.73
B. M.	19 mo.	5,000 q.8h.	.512	.30	.26
			.16	.16	.125
C. M. C.	4	5,000 q.8h.	.26	.45	.58
		Average	.500	.456	.321

are modified by the fluid intake, relationship to meals, and other individual unknown factors. A combined tablet,* containing 100,000 units of potassium penicillin with 250 mg. of Benemid, was given to twenty patients and serum penicillin levels were determined at one, two, and three hours. The dosage was 3,000 to 5,000 units of penicillin per pound of body weight (approximately 6,000 to 11,000 units per kilogram) every six to eight hours given approximately one hour before meals. The penicillin levels (Table II) were remarkably constant in this series and the levels were higher and decreased at a slower rate than is observed with oral penicillin alone.[14] One hundred per cent of patients studied had a three-hour penicillin plasma level above .03 unit per milliliter and the average was tenfold higher than the minimum inhibitory level for the beta-hemolytic streptococcus encountered in scarlet fever.[14] Repeat levels on seven children up to the seventh day on this medication did not suggest that the serum penicillin level was cumulative. Spot Benemid levels in four patients at three, four, or five hours after the dose varied between 8.4 and 13.2 mg. per milliliter. No evidence of toxicity or gastrointestinal incompatibility was observed. Seven of these children had beta-hemolytic streptococci in their throats on admission. Daily cultures became negative for streptococci within two days or less after the penicillin-Benemid tablet was started. All children showed prompt clinical improvement.

*"Remanden" kindly supplied by Sharp & Dohme, Inc.

SUMMARY AND CONCLUSIONS

In a study of eighty-five children the optimal oral dose of Benemid was found to be an initial dose of 25 mg. per kilogram of body weight followed by 10 mg. per kilogram every six hours for maintenance therapy. For children of over 50 kilograms of body weight the adult dose is adequate, 500 mg. every six hours following an initial dose of 1 to 2 Gm. if rapid action is desired.

Following a single intramuscular injection of crystalline penicillin of 10,000 units per kilogram of body weight, the blood levels in a patient receiving adequate doses of Benemid fall at such a rate that bacteriostatic levels are maintained for eight to ten hours. At two to three hours after the injection the level of penicillin in the blood of the patient receiving Benemid is five to tenfold higher than in that of the same patient without Benemid.

This slow excretion of penicillin permits cumulation, and very high blood levels may be maintained if repeated doses of penicillin and Benemid are given. Examples are given of clinical application of this principle.

By trial-and-error variation of the dosage and by theoretical calculation the effect of Benemid on penicillin excretion in children seems to correlate roughly with what would be expected if it interfered with tubular excretion without influence on glomerular filtration of penicillin.

Average penicillin serum levels in twenty children who received an oral tablet (Remanden) containing potassium penicillin and Benemid were as follows: one hour, 0.500 unit per milliliter; two hours, 0.456 unit per milliliter; three hours, 0.321 unit per milliliter.

Using the combined penicillin-Benemid oral tablet, a dose of 6,600 units of penicillin per kilogram of body weight every eight hours should give blood levels well above those necessary to control most infections which are sensitive to penicillin.

No significant evidence of toxicity from Benemid was observed in these infants and children.

REFERENCES

1. Beyer, K. H., Wiebelhous, V. D., Tillson, E. K., Russo, H. F., and Wilhoyte, K. M.: Benemid p-(di-n-propylsulfamyl)-Benzoic Acid; Inhibition of Glycine Conjugative Reactions, Proc. Soc. Exper. Biol. & Med. **74**: 772, 1950.
2. Beyer, K. H., Wiebelhous, V. D., Russo, H. F., Piek, H. M., and McKinney, S. E.: Benemid p-(di-n-propylsulfamyl)-Benzoic Acid an Anticatabolite: Its Pharmacological Properties, Fed. Proc. **9**: 258, 1950.
3. Boger, W. P., Beatty, J. O., Pitts, F. W., and Flippin, H. F.: The Influence of a New Benzoic Acid Derivative on the Metabolism of Para-aminosalicylic Acid (PAS) and Penicillin, Ann. Int. Med. **33**: 18, 1950.
4. Boger, W. P., Matteucci, W. V., and Beatty, J. O.: Benemid p-(di-n-propysulfamyl)-Benzoic Acid: Lack of Effect on Aureomycin, Chloromycetin, Streptomycin and Terramycin, Proc. Soc. Exper. Biol. & Med. **76**: 222, 1951.
5. Gutman, A. B.: Uric Acid Metabolism and Gout, Am. J. Med. **9**: 789, 1950.
6. Gutman, A. B.: Some Recent Advances in the Study of Uric Acid Metabolism and Gout, Bull. New York, Acad. of Med. **27**: 144, 1951.
7. Boger, W. P., Mattucci, W. V., Schimmel, N. H., and Flippin, H. F.: Benemid, Its Influence on PAS, Penicillin and Other Antibiotics, Scientific Exhibit at American Medical Association Session, June 11-15, 1951.
8. Waldo, J. F.: Penicillin Blocking Agents, J. Omaha Mid-West Clin. Soc. **12**: 17, 1951.
9. Hildick-Smith, G., and Fell, M. B.: A Micromethod for Blood Penicillin Assay, J. Lab. & Clin. Med. **34**: 1687, 1949.
10. Corneal, B. F., Hildick-Smith, G., Fell, M. B., and Scott, T. F. McNair: The Evaluation of an Effective Dosage of Caronamide (4-Carboxyphenylmethanesulfonanilide) for the Suppression of Tubular Excretion of Penicillin in Children, J. Clin. Investigation **27**: 628, 1948.
11. Tillson, E. K., Schuehardt, G., Pitt, A., Gass, R. W., and Beyer, K.: Benemid p-(di-n-propysulfamyl) Benzoic Acid an Anticatabolite: Its Estimation in Body Fluids, Fed. Proc. **9**: 320, 1950.
12. Eagle, H., and Newman, E.: The Renal Clearance of Penicillin F, G, K, X in Rabbits and Man, J. Clin. Investigation **26**: 903, 1947.
13. Boger, W. P.: Personal communication.
14. Weinstein, L., and Perrin, T. S.: The Treatment of Scarlet Fever With Penicillin G Administered Orally Three Times a Day, J. PEDIAT. **37**: 844, 1950.

IMMUNIZATION OF NEWBORN INFANTS WITH PERTUSSIS VACCINE

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IN THE first part of our study, expectant mothers were immunized with saline pertussis antigen in the first and third trimesters of pregnancy. Bloods were drawn on the pregnant women before immunization with the pertussis vaccine and at delivery, as were cord bloods. Agglutinin titers were determined. The observations indicated that a protective level of pertussis agglutinins does not occur in the average pregnant woman. When saline-prepared vaccine was used to immunize the expectant mothers, a significant number of mothers and newborn infants became immunized as indicated by the agglutinin titers of blood drawn from mothers at delivery and the cord bloods. There was no significant difference in the agglutinin titers produced in the infants whether the mothers were immunized in the first or third trimester of pregnancy.

It is an accepted fact that pertussis has its most serious morbidity and mortality in infants under 6 months of age. In the second part of our study, we attempted to determine whether an adequate protective level of pertussis agglutinins can be obtained in newborn infants by immunizing them without injurious effects. The pertussis agglutinin level was used as the measure of the infant's ability to form antibodies, although it is recognized that this may not necessarily correspond with clinical immunity.

Baumgartner[1] was of the opinion that infants under 6 months of age could not produce sufficient antibodies due to their physiological immaturity. Accepting this view, Sauer[2] recommended that infants should be immunized after 7 months of age. Subsequently, Sauer reported that when alum-precipitated pertussis vaccine is used at 3, 4, 5, and 6 months of age, adequate protection against pertussis is obtained. Peterson and associates[3] in 1942 demonstrated that young infants could be protected against pertussis. This was confirmed by Sako[4] in 1945. Peterson and Christie[5] injected eighty billion alum hydroxide adsorbed phase one *Hemophilus pertussis* organisms in young babies and produced satisfactory immunity in 73 to 79 per cent. They suggested that with the injection of a larger number of organisms greater protection in a higher percentage of cases was possible.

Miller and co-workers[6] immunized infants at 5 days, 1 month, and 2 months of age with a total of fifty billion saline suspended organisms. However, at 3 months of age only 15.4 per cent showed significant protective agglutinins. When one hundred billion saline suspended cells were used, 25.2 per cent showed a good response. When injections of eighty billion or-

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ganisms were used given in divided doses at 1, 2, and 3 months of age, 48.5 per cent attained protective agglutinin titer one month after the last injection. During the next six months, only 36.4 per cent showed adequate protective titers. In older infants, 60 per cent maintained a high titer for four years. However, with alum-precipitated pertussis vaccine a high titer was produced in 62.6 per cent and maintained in 60 per cent for one year.

Di Sant' Agnese[7] also demonstrated that a significant degree of protection can be attained in newborn infants, with best results in the young infant and older child.

Chamberlain and Bullock[8] gave a combined diphtheria, pertussis, and tetanus vaccine to newborn infants and showed that these infants attained high titers of pertussis agglutinins.

METHOD OF STUDY

This study was carried out at the Beth-El Hospital. One hundred seventeen newborn infants were injected with pertussis vaccine at 4, 8, and 12 weeks of age. A booster was given at 9 months of age.

The patients were divided into two groups. One group received saline pertussis vaccine which contained twenty billion organisms per cubic centimeter.* The dosages were 1, 1.5, and 1.5 c.c. The total dosage injected was eighty billion organisms. At 9 months of age a booster of 1 c.c. was given.

The second group of infants received a specially prepared soluble detoxified alum-precipitated pertussis vaccine containing forty billion organisms per cubic centimeter.* This product was a detoxified alum-precipitated soluble antigen but did not contain the toxin. The intervals of injection were the same as in the first group. The dosages were 0.5, 0.75, and 0.75 c.c. A total of eighty billion organisms was injected. A booster of 0.5 c.c. was given at 9 months of age.

Blood specimens for the determination of pertussis-agglutinin levels were taken just before the pertussis immunization series and three months after the last injection. In some patients we were able to obtain a blood specimen at 9 months of age, at 1 year, and at 18 months of age. A titer of 1:80 or higher signified sufficient antibody present against pertussis.

RESULTS

Of our 117 patients, only four showed an adequate pertussis agglutinin titer preceding the pertussis antigen series. Three had a titer of 1:80 and one had a titer of 1:640. The greatest number of titers at one month of age were negative at 1:10 dilution. Twenty-two infants received saline-suspended vaccine. Thirteen of these showed significant pertussis agglutinins in the blood three months after the series. In no case, however, was the titer much above the minimum protective level.

Twenty-two babies received the soluble detoxified alum-precipitated vaccine. All of these developed protective agglutinin levels and in eighteen the titer was above 1:1,280. Ten returned at 9 months of age and still showed an adequate agglutinin titer. Reactions to the injections were minimal. When they occurred, they con-

*This vaccine was prepared by the New York City Health Department.

*Vaccine supplied by Sharp & Dohme, Inc.

sisted of fever, irritability, and mild local reactions.

SUMMARY AND CONCLUSIONS

1. Newborn infants are practically devoid of any pertussis antibodies.

2. Injections of saline pertussis vaccine given to twenty-two newborn infants at 4, 8, and 12 weeks of age produced satisfactory pertussis agglutinins in thirteen. These titers, although adequate, were not high.

3. Injections of soluble detoxified alum-precipitated pertussis vaccine given to twenty-two newborn infants at 4, 8, and 12 weeks of age produced satisfactory pertussis agglutinin titers in all babies. In 90 per cent, the titers were high.

The cooperation of the laboratory staffs of Beth-El Hospital and of Sharp & Dohme, Inc., is greatfully acknowledged.

REFERENCES

1. Baumgartner, L.: The Relationship of Age to Immunological Reactions, Yale J. Biol. & Med. 6: 403, 1934.
2. Sauer, L. W.: The Age Factor in Active Immunization Against Whooping Cough, Am. J. Path. 17: 719, 1941.
3. Keller, A. E., Peterson, J. C., and Denson, P. M.: Opsonocytophagic Reaction to Whooping Cough Vaccination, Am. J. Pub. Health 32: 240, 1942.
4. Sako, W., Treuting, W. L., Witt, D. B., and Nichamin, S. J.: Early Immunization Against Pertussis With Alum-Precipitated Vaccine, J. A. M. A. 127: 379, 1945.
5. Peterson, J. Cyril, and Christie, Amos: Immunization in the Young Infant, Response to Combined Vaccines I-IV, Am. J. Dis. Child. 81: 4, 1951.
6. Miller, J. J., Jr., Faber, H. K., Ryan, M. L., Silverberg, R. J., and Lew, E.: Immunization Against Pertussis During the First Four Months of Life, Pediatrics 4: 468, 1949.
7. di Sant' Agnese, P. A.: Simultaneous Immunization of Newborn Infants Against Diphtheria, Tetanus, and Pertussis: Production of Antibodies and Duration of Antibody Levels in Eastern Metropolitan Area, Am. J. Pub. Health 40: 674, 1950.
8. Chamberlain, H. D., and Bullock, R. E.: Ohio State M. J., Sept., 1950.

A STUDY OF THE ERYTHROCYTE SEDIMENTATION RATE FOR WELL CHILDREN

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THE sedimentation rate (ESR) is widely used as a diagnostic aid although its normal variation and accuracy, or its clinical significance, have never been clearly established. The "normal" ESR for well children has been accepted on a paucity of investigative information. Thus "normals" for the Cutler and Smith techniques have been reported[1] and accepted[2, 3, 4] though derived from data obtained on as few as twenty-four well children (age group 5 months to 7 years); "normals" for the Landau method on data[5] from only seventy-four children (age group 3 to 10 years). The Wintrobe method, although popularly used throughout the country, has never been thoroughly evaluated as applied to children.[6] In addition, variations have been made in many techniques by substituting anticoagulants for those originally recommended, without adequate knowledge of the effects of such substitutions on the final result. Last, few thorough studies are available with respect to the reproducibility (reliability) of the ESR as determined on multiple aliquots of one blood specimen by the same technique.

The purposes of these studies were to:

1. Determine the normal of sedimentation rates for well children between the ages of 4 and 15 years utilizing two well-known techniques (Wintrobe macromethod and Landau-Adams micromethod).

2. Determine the packed cell volume (PCV) for well children.

3. Note the effect on the ESR of substituting other anticoagulants for those recommended for the original method.

4. Determine and then to compare the reliability of each of three methods (Wintrobe and Westergren macromethods and Landau-Adams micromethod).

5. Accumulate and review data which would serve as a valid basis upon which to judge the limitations of the use of the ESR as a guide to clinical activity of the disease process being studied.

METHODS

Techniques.—The original Wintrobe-Landsberg,[7, 8] Landau-Adams,[5, 9] and Westergren[10] methods for the determination of the ESR, and of the PCV[7] were followed. All tests were initiated at room temperature, within fifteen minutes to one hour of drawing the blood specimen. The value of the ESR was recorded at the end of one hour from the time of starting the test. Every effort was made to eliminate all reported technical errors.[11] Dry, sterile syringes were used in order to prevent the highly depressant effect on the ESR of residual liquid in alcohol-rinsed syringes.[12] The es-

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sential technical details of the methods of determination of ESR are summarized in Table I.

Reliability of Techniques.—In order to discover the greatest reliability (reproducibility) of a given technique, it is essential that one skilled technician perform, in immediate sequence and under controlled conditions, several (i.e., replicate) determinations on a single blood specimen.[13] In this study thirty such replicate determinations of the ESR were made by the Westergren technique on a single, rapidly sedimenting, venous blood specimen, and thirty more on a less rapidly sedimenting venous specimen. This entire procedure was repeated with the Landau-Adams and with the Wintrobe (uncorrected) techniques. The number (N) of replicate determinations was set at thirty, the minimum which would ensure reliable statistical data on variability within a

TABLE I. TECHNICAL DETAILS FOR METHODS

METHOD (ORIGINAL)	ANTICOAGULANT		REMARKS ON TECHNIQUE ALL TESTS READ AT ONE HOUR AND AT ROOM TEMPERATURE 19 TO 26°C.
	ORIGINAL	MODIFICATION	
Wintrobe-Landsberg[8]	*Wintrobe-dry: 4.0 mg. $K_2C_2O_4 \cdot H_2O$ and 6.0 mg. $(NH_4)_2C_2O_4 \cdot H_2O$ dissolved in 0.5 ml. distilled H_2O, placed in 2 dram vial, oven dried below 80° C.	None	5.0 ml. of blood, obtained by venipuncture, was delivered into the vial containing the anticoagulant and mixed by inversion The PCV was read after centrifugation (35 min. at 2,200 r.p.m.; 1065G) and recorded for use in correcting the ESR[7]
Westergren[10]	1.25 ml. of 3.8% citrate solution ($Na_3C_6H_5O_7 + 5\frac{1}{2}H_2O$) in distilled H_2O in a two dram vial	*Wintrobe-dry substituted	Blood specimen as above
Landau-Adams[5, 9]	5% citrate solution ($Na_3C_6H_5O_7 + 5\frac{1}{2}H_2O$) in distilled H_2O	*Wintrobe-dry, mixed with venous blood, is substituted for capillary blood alone	Landau-Adams aspirator used to draw citrate to first line encircling pipette, then to draw blood (from finger puncture) until combined column reaches second line, to mix blood and citrate by drawing into bulb 3 times, and to bring top of column to scale zero

*See explanation following "Wintrobe-dry" under "Anticoagulant-Original."

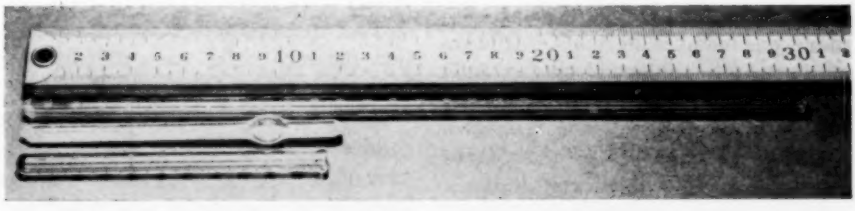


Fig. 1.—Illustration of three types of sedimentation tubes: Westergren (300 mm.), Landau-Adams (120 mm. with bulb in tube) and Wintrobe (112 mm.).

method.[14] It was not considered necessary to test both capillary (arterial) and venous blood specimens, since the sedimentation rate has been shown not to differ significantly for arterial and for venous blood from the same patient.[1, 15]

The reliability of the Wintrobe method of determination of the PCV was not investigated, since this had been established as 2.5 per cent on either side of a single reading,[16] and the same value (2.5 per cent) had been found for the Van Allen PCV.[17]

Anticoagulants.—The comparison of anticoagulants was based on the ESR as determined on paired blood specimens. These specimens were drawn in immediate sequence from the same child or two aliquots of the same specimen were used. A determination of ESR was made by one of the methods cited.[5, 8, 9, 10] At the same time, the ESR of the paired specimen was determined by one of these same methods, modified by changing the anticoagulant. Thus, the Westergren technique was modified, in this study, by substitution of the Wintrobe-dry potassium-and-ammonium-oxalate for the 3.8 per cent citrate solution of Westergren. The Landau-Adams technique was modified by the substitution of venous for capillary blood (obtained by finger puncture) and by mixing the blood specimen with the Wintrobe-dry anticoagulant before addition of Landau's 5 per cent citrate solution.

Clinical Material.—The children in the study were enrolled in certain schools* in San Francisco, Calif. (designated as Group 1), or in the San Francisco Cardiac Center (designated as Groups 2 and 3).

Group 1 was composed of well school children in whom no illness was suspected by the school physician. The blood specimens were drawn by a physician and a brief medical history, designed to exclude those children reporting recent colds or upper respiratory infections, was taken the same day. If the ESR was elevated (21 mm. or more, Wintrobe, uncorrected), a second ESR was determined for the same child a year later. If the second rate was elevated, the child reported to a pediatrician or internist at the San Francisco Cardiac Center for a complete examination. On the basis of this examination, subsequent visits, and a battery of laboratory tests, the physician classified such children as "well" (Group 1) or as "not well." The ESR was included in the data on normals for Group 1 only if obtained for a child finally designated as Group 1 (well school children).

Group 2 was composed of all children enrolled in the San Francisco Cardiac Center* from Sept. 15, 1950, to April 15, 1952. After a complete medical examination, a final classification for each child was made by the pediatrician or internist.

Group 3 was composed of all those children (at the above center) who were classified by the pediatrician or internist as having no detectable illness, and who were diagnosed as having a "functional heart murmur." By "functional heart murmur"[18] is meant an adventitious sound (heard over the heart) which does not signify organic illness. A child with a functional heart murmur is considered completely well, the detectable murmur being

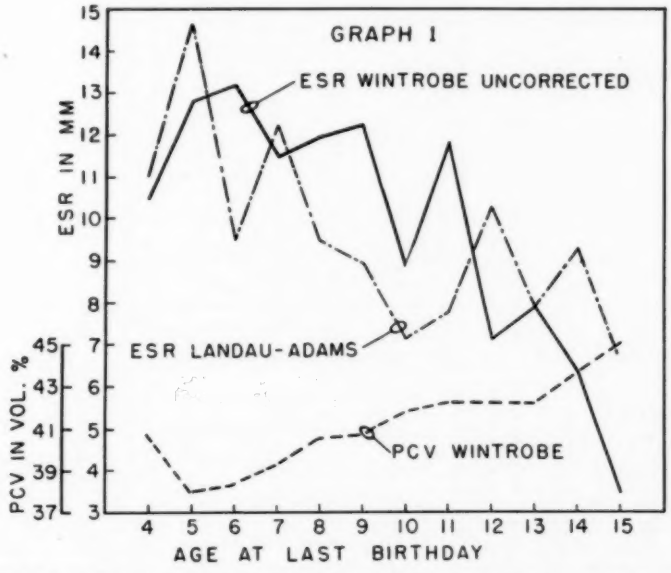
*Blood collected through the cooperation of Dr. J. C. Geiger, then Health Officer of San Francisco; Dr. Paul S. Barrett, Director, Bureau of Child Hygiene, City and County of San Francisco; Doris L. Robinson, Director of Public Health Nursing, San Francisco Department of Public Health; Mary Huston, R.N., Public Health Nurse, Hooper Foundation; and Dr. Herbert C. Clish, Superintendent of San Francisco Schools.

merely a nonpathological finding which has no relation to disease of the heart.

RESULTS

The ESR in Well Children.—The Wintrobe uncorrected values for ESR as determined on well children (Group 1) range from 1 to 40 mm., as shown by the frequency distribution for ESR on year of age (Table IIA). In Table IIB, several statistical computations for these data are summarized. Age groupings for the ESR data were chosen so as to ensure the greatest uniformity within groups and the most reliable difference between groups. Inspection of Graph 1 indicated that the choice of a cutting point between 11 and 12 years would be most likely to meet these criteria. Calculation of the standard deviations (S.D.), and of the critical ratios[19] (as indices of the reliability of differences between means) for several different age groupings supported this choice. The data were, therefore, grouped for children from 4 through 11 years of age and, separately, for children from 12 through 15 years of age.

Since the frequency distribution for the ESR (Wintrobe, uncorrected) in Group 3, "well children, functional," is almost identical[20] with the frequency distribution data for Group 1, only the summary data are presented in Table III. This table also lists, as determined by the Landau-Adams method, an analysis of ESR data for Group 3. The PCV for Group 1, "well school children," is also shown, in case a correction of the Wintrobe ESR is desired.



Graph 1.—ESR in millimeters and PCV in volume per cent for well children.

Anticoagulants.—It may be concluded that neither substitution of dry oxalates for citrate solution nor addition of oxalated blood to citrate solution resulted in any significant change in the value of the ESR from that ob-

TABLE IIA. ERYTHROCYTE SEDIMENTATION RATE FREQUENCY DISTRIBUTION ON AGE

AGE IN YEARS AT LAST BIRTHDAY	TOTAL WELL CHILDREN	ERYTHROCYTE SEDIMENTATION RATES, WINTROBE UNCORRECTED, FOR WELL SCHOOL CHILDREN (GROUP 1), READ, AT END OF ONE HOUR, AS MM. DROP																																
		0	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	25	27	29	30	32	34	37	38	39
ALL AGES	293	1	7	14	19	19	30	15	18	12	22	22	17	11	22	10	14	7	6	5	4	1	1	4	1	1	1	1	1	2	1	2	1	1
4	7			1		1					1			1	1			1	1															
5	27				1		1		1	1	3	5	2	2	2	1	1	1	1		3			1						1				
6	32					1	4	1	1	1	2	2	3	3	1	1	3	2	2	1		1		1							1	1		
7	32				3	1	1	2	4	1	2	4	1	2	2	3	2			1							1					1		
8	26				3	1	1	2	1	2		3	1		3	2		2		1	1			1		1		1		1				
9	18						2		2		3	2	1	1	3				1	1				1					1					
10	19			2		1	2	2	2		1	1	2		3		3											1					
11	21				1		3	3	1	2	1	1	2	1	1		2		1														
12	36	1	1	4	3	4	6		2		5	1	3	1	2	1	1						1									1	1
13	31			4	2	2	4	3	2	4	2	1	1		1	1	1	1		1				1										
14	32		2	3	4	5	5	1	2		2	2	1		3	1	1																
15	12		4		2	3	1	1		1																								

tained on a paired specimen as tested by the original method of the investigator. This conclusion is based on the high correlation coefficients[21] found. Thus, r was 0.92 for 177 paired sedimentation rates, the first obtained by the original Westergren method, the Adams technique, the other obtained in an identical manner except that venous blood was mixed with Wintrobe-dry anticoagulant before the addition of citrate solution (Table I).

Comparison of Methods.—

Correlation Coefficients, r: When

TABLE IIB. STATISTICAL CONSTANTS FOR ERYTHROCYTE SEDIMENTATION RATES, WINTROBE, UNCORRECTED, FOR WELL SCHOOL CHILDREN (GROUP 1). ESR READ AT END OF ONE HOUR, AS MM. DROP

AGE IN YEARS AT LAST BIRTHDAY	TOTAL WELL CHILDREN	MEAN (M)	RANGE IN mm.	S.D.	SE_M (1.96)	% OF RATES ABOVE 20 mm.
4	7	10.43	2-17	5.74	4.26	0
5	27	12.78	3-32	5.90	2.22	7
6	32	13.16	4-37	7.50	2.60	9
7	32	11.44	3-37	7.45	2.58	9
8	26	11.96	3-32	7.42	2.85	9
9	18	12.22	5-30	6.28	2.90	11
10	19	8.89	2-15	4.38	1.97	0
11	21	11.85	3-39	9.63	4.12	10
12	36	7.05	0-21	4.71	1.54	3
13	31	7.87	2-23	5.13	1.80	3
14	32	6.32	1-15	4.11	1.42	0
15	12	3.42	1-8	2.23	1.26	0

TABLE III. STATISTICAL CONSTANTS FOR ERYTHROCYTE SEDIMENTATION RATE AND PACKED CELL VOLUME FOR WELL CHILDREN

METHODS AND CLASSIFICATION OF CLINICAL MATERIAL	AGE GROUP	TOTAL	MEAN (M)	RANGE IN mm.	S.D.	SE_M(1.96)	% ABOVE 20 mm.
Wintrobe, uncorrected, ESR in mm. per hour for both Group 1 and Group 3 children	4-11	245	12.01	1-41	6.99	0.88	9
	12-15	169	7.49	0-34	5.77	0.86	7
Wintrobe, uncorrected, ESR in mm. per hour for Group 1 children	4-11	182	11.84	2-39	7.08	1.03	8
	12-15	111	6.68	0-23	4.60	0.86	2
Wintrobe, uncorrected, ESR in mm. per hour for Group 3 children	4-11	63	12.54	1-41	6.84	1.69	13
	12-15	73	8.81	1-34	6.81	1.56	5
Landau-Adams ESR in mm. per hour for Group 3 children	4-11	69	9.07	2-24	5.16	1.22	6
	12-15	90	8.30	2-28	5.64	1.18	4
Wintrobe PCV in vol. % for Group 1 children	4-11	182	38.78	32-48	2.88	0.41	--
	12-15	109	42.83	36-50	2.75	0.51	--

second determined in an identical manner, except for the substitution of oxalates (Wintrobe-dry, Table I) for the citrate solution of the original Westergren method. Similarly, r was high for 235 paired ESR values, one obtained by the original Landau-

methods were compared, high correlation coefficients were obtained if the entire range of paired sedimentation rates was considered (Table IV). The highest r (0.94) was obtained by comparing the original Wintrobe (values corrected "for anemia") with the

original Westergren method; the lowest r (0.85) by comparing the modified Landau-Adams technique with the original Westergren method (Table I), 1.00 being a theoretically perfect correlation. Comparably high correlations were found for rates up to 20 mm. per hour. For elevated rates (above 20 mm.) the correlation was not as high (0.73 to 0.86), although for elevated rates the number of values compared was not as great. Too few paired rates were obtained to calculate statistically reliable correlations for certain techniques. The value for r between the ESR obtained by any method used and the Wintrobe corrected values, when compared with the r for rates obtained by the same method and Wintrobe uncorrected values, indicated a difference of only 0.01 or less.

For various levels of the ESR, Graph 2 indicates the per cent of the number of determinations, N, which differed by a given number of millimeters when the paired Wintrobe and Westergren readings were compared. This graph does not show that for rates above 20 mm. (Wintrobe) the Westergren values are often the higher of the two; however, the Westergren value is sometimes the lower even for Wintrobe rates up to 50 mm., according to data obtained in this study.

Reliability: The reliability (reproducibility) of ESR values, as obtained by one technician for twenty-nine to thirty replicate determinations (tests on separate aliquots of one blood specimen by the same technical method under controled conditions), may be estimated for each of three methods from the values presented in Table V.

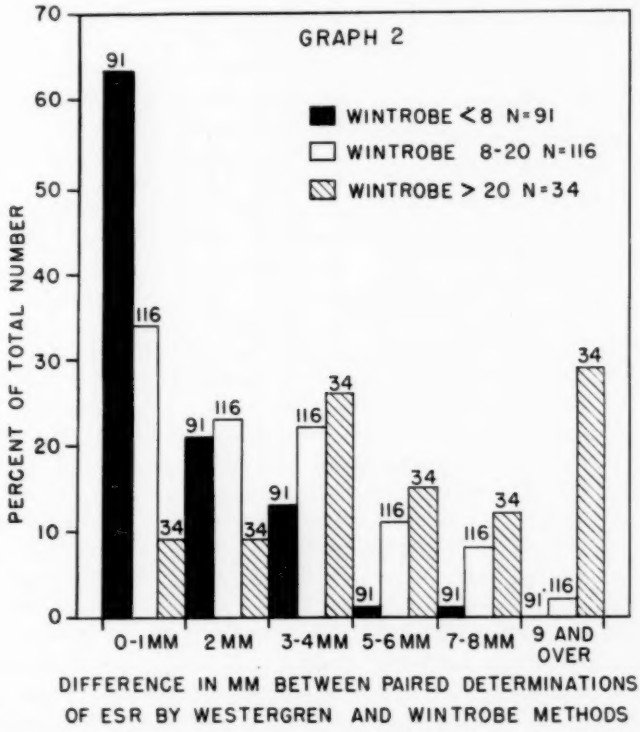
TABLE IV. CORRELATION COEFFICIENTS FOR PAIRED TESTS USING DIFFERENT METHODS OF ESR DETERMINATION
(Values for the ESR Obtained on Paired Specimens of Blood for Children in Group 2)

ESR METHODS COMPARED		NUMBER OF PAIRED TESTS ALL VALUES ESR mm./HR.	r	NUMBER OF PAIRED TESTS ESR 20 MM. OR LESS/HR.	r	NUMBER OF PAIRED TESTS ESR GREATER THAN 20 mm./HR.	r
Wintrobe (corrected) original	Landau-Adams original	252	0.87	228	0.81	24	*
	Landau-Adams modified	345	0.90	310	0.86	35	0.75
Wintrobe (uncorrected) original	Landau-Adams original	252	0.87	223	0.81	29	0.73
	Landau-Adams modified	345	0.90	305	0.86	40	0.79
Wintrobe (corrected) original	Westergren original	179	0.91	175	0.90	4	*
	Westergren modified	241	0.94	209	0.89	32	0.85
Wintrobe (uncorrected) original	Westergren original	179	0.92	150	0.86	29	0.86
	Westergren modified	241	0.93	207	0.89	34	0.85
Landau-Adams original	Westergren modified	63	0.89	62	0.88	1	*
Landau-Adams modified	Westergren original	65	0.85	56	0.80	9	*
	Westergren modified	123	0.85	111	0.77	12	*

*If the number of paired tests was less than thirty, r is not shown.

Confidence Intervals: An ESR report on a single Westergren determination may be considered correct within ±2.2 to ±2.7 mm. for 95 per cent of such reports, as shown by the confidence interval, i.e., [t(S.D.)],[22] at the 0.05 level, and the $N_{28.D.}$[23] value in Table V. Thus, the equal values, 1.04, for $N_{28.D.}$ (the number of tests necessary to guarantee reliability within 2 S.D. limits) indicate that one report should be interpreted within a different ESR range for each method. On the basis of confidence interval, then, a single report obtained by the Westergren technique is the most reliable of the three, the least reliable one report for the Landau-Adams micromethod. For accurate interpretation of a report determined by any of these methods, it would be necessary to consider the value of t(S.D.), the confidence interval.

Standard Deviations: As estimated by 2 S.D. limits, and on the basis of replicate, rather than single determinations, the reliability of the Westergren method was highest, that of the Wintrobe technique next highest, and that of the Landau-Adams micromethod lowest (Table V). It is evident from the values for 2 S.D. that the reports on replicate determinations for the Westergren differ by only 5.3 mm. (for



Graph 2.—The number at the top of each bar indicates the number of paired determinations on which the per cent was calculated.

TABLE V. RELIABILITY OF ERYTHROCYTE SEDIMENTATION RATES

METHOD	BLOOD SPECIMEN	N	MEAN	S.D.	t(S.D.)	2 S.D.	$N_{2S.D.}$	3 S.D.	$N_{3S.D.}$	N_r	F	P
Wintrobe	A	30	10.85	1.21	2.47	2.42	1.04	3.63	.46	6.10	1.782	Less than 0.10 but greater than 0.02
	B	30	30.43	1.62	3.31	3.24	1.04	4.86	.46	10.95		
Landau-Adams vein	A	29	6.10	2.22	4.54	4.44	1.04	6.66	.46	20.61	1.254	Greater than 0.10
	B	30	24.65	1.98	4.04	3.96	1.04	5.94	.46	16.32		
Westergren	C	29	5.90	1.09	2.23	2.18	1.04	3.27	.46	4.97	1.491	Greater than 0.10
	E	30	16.47	1.33	2.72	2.66	1.04	3.99	.46	7.40		

N represents the number of replicate tests on the same specimen.
S.D. represents the standard deviation found for N tests.
t(S.D.) represents the confidence interval.[22] At the 0.05 level of confidence, when N=30, t is equal to 2.042; if N=29, t=2.045.
$N_{2S.D.}$, $N_{3S.D.}$ and N_r represent the number of replications necessary to guarantee that the mean of the results will fall within selected limits 95 per cent of the time, as computed by the formula[23] $\sqrt{N} = \frac{t(S.D.)}{\triangle d}$. The values in column $N_{2S.D.}$ were obtained when $\triangle d$ was arbitrarily set at 2 S.D.; those in column $N_{3S.D.}$, if $\triangle d$ was set at 3 S.D.; those in column N_r, if $\triangle d$ was set at 1 mm.

F represents the variance ratio,[24] i.e., $\frac{(S.D._1)^2}{(S.D._2)^2}$ for twenty-nine or thirty replicate determinations on each of the two blood specimens, and is used to determine P.[24]
P represents the probability that the obtained differences in variance could occur by chance.

results on the same blood specimen as made by one technician). However, the Wintrobe reports differ by 6.5 mm. and the Landau-Adams values by as much as 8.9 mm. at the 2 S.D. level. At the 3 S.D. level this range of values is increased by 3 to 4 mm., according to the method used.

The variance ratio, F[24] (here the ratio of the $[S.D.]^2$ of the ESR for twenty-nine or thirty replicate determinations on the same blood specimen, as compared with the $[S.D.]^2$ of the ESR for twenty-nine or thirty determinations of another blood specimen obtained by an identical technique), was used to find the probability (P)[24] that the obtained differences in variance could occur by chance. The blood specimens were chosen to include those at a low ESR (mean value 6 to 11 mm.) and at a higher ESR (mean value 17 to 30 mm.). The values of P in Table V indicate that there was no difference between the variance of readings at lower, as compared to higher, sedimentation rates obtained by the Westergren method, since P is greater than 0.10. This was also true for the Landau-Adams technique, since P is again greater than 0.10. However, the P value for the Wintrobe (less than 0.10 but greater than 0.02) indicated that P is approaching a level (0.05) where the possibility must be considered that the variance of high values is significantly greater than that of low values.

Packed Cell Volume: The PCV was shown to increase gradually with age (Graph 1). Empirical grouping for uniformity of data on PCV indicated no marked differences in the critical ratio for ages 4 to 11 years as contrasted with that for ages 4 to 12 years. Therefore the same age grouping (4 to 11 and 12 to 15) was used for the PCV as was found most uniform for the ESR, since the PCV was determined for the purpose of correcting the ESR as obtained by the standard Wintrobe method. The statistical analysis of these data is presented in Table II. For the above age groups no significant difference of PCV values was found on the basis of sex, either in this study or in the literature.

DISCUSSION

The reliability of a sedimentation rate, reported for one determination on one patient for one method (Table V), is not as great as may be assumed by the clinician requesting only one test for a given patient on a given day. On the basis of the data presented here, it would appear to be essential that the clinician be aware of the confidence interval and the standard deviation of rates for a given method. In a critical analysis of the reliability of reports, Power[23] suggested that a report based on one determination can be guaranteed only within ±3 S.D. limits. On the basis of 3 S.D., then, one elevated ESR report can be guaranteed within a maximum of ±5 mm. for the Wintrobe technique. Thus, on a given day, if a physician received a single Wintrobe report of 30 mm., it should be interpreted as any value between 25 and 35 mm. A subsequent report of, for example, 25 mm. could be interpreted as a drop of as much as 15 mm. or, equally well, could be interpreted as no change at all. To obtain a valid difference of 1.0 mm., it would be necessary to do eleven tests on each day on each patient (N_r, Table V),[23] which obviously, in most cases, would not be practical. The physician, then,

can interpret an apparent decrease in the ESR only in the light of the reliability of the method. According to the results of these studies, one ESR, reported for the Landau-Adams technique as 25 mm., should be interpreted as any value from 19 to 31 mm.; one Westergren report of 17 mm. interpreted as any value from 13 to 21 mm., for ninety-nine per cent of the reports of Westergren readings has been attributed to two factors: the height and diameter of the tube, which prevents packing at elevated rates,[27] and the dilution of the blood with a salt solution.[26] These two factors apparently operate to increase the elevated ESR, since, for the findings of four investigators,[27, 28, 29, 30] Westergren rates are considerably higher than Wintrobe

TABLE VI. STATISTICAL CONSTANTS FOR ERYTHROCYTE SEDIMENTATION RATES
Values Published for Well Children and Values Found in This Study (in mm./hr.)

METHOD	YEAR PUBLISHED	AGE GROUP	NUMBER OF CHILDREN	MEAN	RANGE IN mm.	S.D.	SE_M (1.96)
Wintrobe, uncorrected for both Group 1 and Group 3 children	*1953	4-11	245	12.01	1-41	6.99	0.88
		12-15	169	7.49	0-34	5.77	0.86
Landau-Adams for Group 3 children	*1953	4-11	69	9.07	2-24	5.16	1.22
		12-15	90	8.30	2-28	5.64	1.18
Landau (Linzenmeier-Raunert)	1933[5]	6-15	87	3.76	1-8	†	†
Westergren	1926[38]	Less than 18	†	†	4-7	†	†
		4-11	87	11.53	1-62	11.74	1.78
	1939[39, 40]	12-14	62	11.56	1-60	10.55	2.63
	‡1939[37]	m12-19	3,101	5.54	†	3.52	0.12
		f12-16	1,648	10.94	†	6.28	0.29
		T12-19	4.749	7.41	†	5.33	0.16
Smith	1936[1]	4-11	23	9.13	3-13	2.82	1.16
Cutler	1936[1]	4-11	23	8.52	4-13	2.39	0.98
Cutler, with correction for anemia	1944[41]	10-11	43	8.70	4-25	3.67	1.10
		12-19	259	8.25	2-23	3.90	0.47
Ström	1938[17]	8 and 11	117	11.23	2-19	4.24	0.86
Rourke-Ernstene modified heparin anticoagulant	1942[42]	11-17	100	m0.4§ f0.6	0.9-2§	†	†

*Table III, this study.
†Published data insufficient for this calculation.
‡Korean and Japanese children.
§Readings in mm. drop per minute during period of constant fall.
m = male.
f = female.
T = Total.

received. Of these three ESR techniques, then, it is evident that the Westergren is the most reliable.

The basic theory of blood sedimentation is now in a state of "undoubted academic elegance but of doubtful practical value."[25] Nevertheless, the superior reliability of the Westergren technique, as shown above, has been demonstrated on an empirical basis by Berg.[26] The comparative uniformity rates above 20 mm. In this study, however, the Westergren readings were often but not always higher, even for Wintrobe values up to 50 mm. The Westergren readings were also higher than those of the Hellige-Vollmer[31] (Langer) and the Kato[32] rates for micromethods above 20 mm.; but not consistently higher above 30 mm. for the Ström[33] micromethod, nor for the Landau-Adams (this study).

With respect to anticoagulants, as judged by the ESR for paired specimens, substitution of a proper concentration of a dry oxalate mixture for a citrate solution had little effect on the ESR obtained (Table IV). However, the findings of both Berg[26] and Nichols[34] indicated that the test must be initiated within one hour after the blood is drawn if dry anticoagulants were used, whereas the ESR usually remained constant up to four hours if the blood was diluted with isotonic salt solution. Also, Nielsen[35] found that substitution of heparin for citrate solution made little difference in the Westergren ESR, provided the same blood dilution was used.

The "normal" ESR for well children, then, must be evaluated in terms of the reliability of the method used, the dilution of the blood specimen, and the time interval between withdrawal of blood and the initiation of the determination.

In these studies, significantly different mean values of the ESR for age groups 4 to 11 years and 12 to 15 years were found for "normal" well children, when the Wintrobe technique was used (Table III). No such statistical difference in mean values of the ESR could be established on the basis of sex.[36] Kitamura,[37] however, found a mean of 5.5 mm. for boys and 10.9 mm. for girls for Westergren determinations for 4,749 Korean and Japanese children (Table VI). Additional techniques and findings, which were quite varied, may be readily compared from the statistical constants on ESR which are presented in Table VI. Values in this table are in conformity with the conclusions of certain investigators[43] who consider that mean values of "normal" for some ESR methods are statistically different. A careful study of Table VI will indicate that the range of "normal" values in well children is very broad, i.e., 1 to 60 mm. for the Westergren, 1 to 41 mm. for the Wintrobe, and 2 to 28 mm. for the Landau-Adams. Even if only 95 per cent of all rates are considered, the values for two S.D. indicate that the upper limit of "normal" is as high as 22 mm. above the mean (Westergren). Consideration of the data in Tables V and VI leads to the conclusion that, for a given method, the mean "normal" ESR in well children is of clinical significance only when the range or the 2 S.D. value and the reliability of that method is known. It appears extremely doubtful that one laboratory report, based on any technique listed, should be considered above the upper limit of "normal" for well children unless this upper limit is fairly high, perhaps 20 mm. For the Wintrobe ESR, the selection of even 20 mm. as the upper limit of "normal" eliminates up to 11 per cent of the values for well children in the age group 4 to 11 and up to 3 per cent of the values for well children of 12 to 15 years (Table IIB).

Correction "for Anemia." — The well-established practice of correcting the ESR "for anemia" on the basis of PCV appears to be unnecessary on the basis of the correlation coefficients, r, of the ESR obtained by the Wintrobe and other techniques, there being no significant difference in r for corrected and uncorrected rates (Table IV). Mahoney and associates[44] did not correct the Wintrobe-Landsberg ESR in a series of 2,703 paired readings for which a high correlation (0.94) was obtained with the Rourke-Ernstene ESR. The investigations of Gilmour and Sykes,[28] of Hynes and

Whitby,[45] and of Gibson[46] indicate that a correction "for anemia" is not valid. Terry,[47] McFarlane and O'Brien,[25] and Sinton[48] agree with Alston[11] that this is a "false method of simplification." The weight of evidence cited appears to be in agreement with the statement that a correction for anemia is unnecessary and may be misleading. Nevertheless, the PCV, as obtained here and as recorded in the literature, is listed in Table VII. The PCV values are listed for use in correction of the ESR, in case a corrected value is preferred and as published by Osgood and Baker,[54] P in each case being greater than 0.10.

The "inclined tube" method for determination of ESR has not been utilized in this study although it has been reported as extremely useful in Europe.[55] If the sedimentation tube is inclined at 45°, the sedimentation rate is greatly increased, the reading at the end of fifteen minutes having a high correlation with the reading at the end of an hour for a vertical Westergren tube[56] (unless the hour reading is below 2 mm.). Although r is high, a different "normal" must be

TABLE VII. STATISTICAL CONSTANTS FOR PACKED CELL VOLUME
Values Published for Well Children and Values Found in This Study

METHOD	YEAR PUBLISHED	AGE GROUP	NUMBER OF CHILDREN	MEAN	RANGE IN VOL. %	S.D.	SE_M (1.96)
Wintrobe	1953*	4-11	182	39.78	32-48	2.88	0.41
		12-15	109	42.83	36-50	2.75	0.51
	1936[49]	4-11	282	40.69	†	3.38	0.39
	1938[50]	12-20	200	44.95	38-53	3.18	0.43
Hamre pipette	1940[51]	3-6	179	40.5	29-56	4.64	0.69
Smith	1938[52]	2-12	30	39.34	†	2.68	0.84
Smith, with 5% sodium citrate	1936[1]	4-11	20	36.60	32-40	2.16	0.94
Smith, modified with heparin	1936[1]	4-11	21	43.86	40-47	2.03	0.86
Van Allen	1938[53]	8 & 11	71	40.80	†	1.81	0.41
Haskins	1935[54]	4-11	175	35.71	29-42	2.38	0.35

*Table III, this study.
†Published data insufficient for this calculation.

as a guide in the clinical interpretation of the PCV reported for children tentatively diagnosed as having polycythemia (borderline cyanosis), anemia, congestive heart failure, etc. A single mean value for PCV, calculated from values for both males and females, is given in Table VII, since no significant statistical difference in the mean PCV for males and females could be established for the Wintrobe PCV (as found in this study), for the Van Allen PCV as published by Faergeman,[53] or for the Haskins PCV established, since the rates are not equal due to the packing of erythrocytes in the inclined tube.[57, 58] There is no doubt, however, that as a screening technique for elevated rates the inclined tube is an excellent and rapid method.[59, 60, 61, 62]

CONCLUSIONS

From the results of this study and a survey of the available literature the following conclusions are drawn.

1. The normal sedimentation rate for children 4 to 15 years of age,

regardless of sex, is from 0 to 20 mm. per hour Wintrobe uncorrected; however, 5 to 10 per cent of apparently well normal children may have a sedimentation rate higher than 20 mm. per hour.

2. In general, children in the age group 4 to 11 years have a higher average Wintrobe sedimentation rate (12 mm. per hour) than children 12 to 15 years of age, who have an average sedimentation rate of 7.5 mm. per hour, a value almost identical with that obtained for adult males in other related studies of the Wintrobe method.

3. The normal ESR (as determined at the end of one hour) by the Landau-Adams micromethod for children 4 to 15 years of age is also 0 to 20 mm.; nevertheless 5 per cent of apparently well normal children may have a sedimentation rate of over 20 mm.

4. The correlation of sedimentation rates determined in immediate sequence for the same child by the Wintrobe, Westergren, or the Landau-Adams methods is extremely high as indicated by the correlation coefficients; one may thus use any one of these three methods with the knowledge that results will be similar.

When p r o p e r l y performed, the micromethod (Landau-Adams) may be used to determine the sedimentation rates of children, since findings by this micromethod are quite comparable to those of the two macromethods studied.

5. The type of anticoagulant used makes little, if any, difference in the final result, i.e., the substitution of dry oxalates for citrate solution may be made, provided the determination of the sedimentation rate is initiated within one hour after the blood specimen is drawn.

6. If thirty sedimentation tests are made on one sample of blood by the same method, variable results will be obtained. Hour readings for the Wintrobe method will vary by as much as ±5 mm.; for the Landau-Adams micro technique by as much as ±7 mm., and for the Westergren technique by as much as ±4 mm. Therefore, the accuracy of a single report must be interpreted with respect to these variations.

7. Correction of the Wintrobe ESR for anemia may not be necessary, since the correlation of corrected and uncorrected ESR by this method is extremely high (.95).

8. The PCV for well children 4 to 15 years of age increases gradually with year of age. The average PCV, as determined in volume per cent by the Wintrobe technique, is 40 per cent for well children 4 through 11 years of age, and 43 per cent for those 12 through 15 years of age, regardless of sex. Consideration of the computations from PCV data obtained in this study and from the PCV data recorded by certain other investigators, given in Table VII with respect to the mean, range, S.D., and SE_M (1.96) of four other methods, indicates that these constants are not the same for all methods.

9. Consideration of the computations from ESR data obtained in this study and from the ESR data recorded by certain other ingestigators, given in Table VI with respect to the mean, range, S.D., and SE_M (1.96) of several other methods, indicates that these constants are not the same for all methods.

10. From all of the foregoing it can readily be seen that determination of the ESR in children may not be a

highly accurate means of studying activity in any single disease; that limitations with respect to the accuracy of a single ESR must be recognized and the clinical interpretation determined with a full knowledge of the variabilities of the sedimentation rate in well children.

REFERENCES

1. Smith, C. H.: A Method for Determining the Sedimentation Rate and Red Cell Volume in Infants and Children With the Use of Capillary Blood, Am. J. M. Sc. **192**: 73, 1936.
2. The National Research Council, Committee of the American Institute of Biological Sciences. *Standard Values in Blood* (AF Tech. Report No. *6039*), E. C. Albritton, ed., July, 1951.
3. Behrendt, H.: Diagnostic Tests for Infants and Children, New York, 1949, Interscience Publishers, Inc., p. 482.
4. Sunderman, F. W., and Boerner, F.: Normal Values in Clinical Medicine, Philadelphia and London, 1949, W. B. Saunders Co., p. 48.
5. Landau, A.: Microsedimentation (Linzenmeier-Raunert Method). Its Serviceability and Significance in Pediatrics; Use of a Modified Apparatus With Simplified Technique, Also Serviceable in Ambulant Practice, Am. J. Dis. Child. **45**: 692, 1933.
6. Wintrobe, M. M.: Personal communication, 1948.
7. Wintrobe, M. M.: Clinical Hematology, Philadelphia, 1951, Lea & Febiger, pp. 289-290.
8. Wintrobe, M. M., and Landsberg, J. W.: A Standardized Technique for the Blood Sedimentation Test, Am. J. M. Sc. **189**: 102, 1935.
9. Package insert for Landau-Adams Microsedimentation apparatus.
10. Westergren, A.: Studies of the Suspension Stability of the Blood in Pulmonary Tuberculosis, Acta med. scandinav. **54**: 247, 1921.
11. Alston, J. M.: Methods of Estimating the Blood Sedimentation Rate, Practitioner **157**: 23-27, 1946.
12. Sykes, W. O.: Erythrocyte Sedimentation Rate, The Effect of Alcohol as Contaminant, Brit. M. J. **1**: 393, 1948.
13. Liebhafsky, H. A., Pfeiffer, H. G., and Balis, E. W.: Statistical Operating Rule for Analytical Chemists, Anal. Chem. **11**: 1531, 1951.
14. McNemer, Q.: Psychological Statistics, New York, 1939, John Wiley & Sons, Inc., p. 216.
15. Cerroni, L.: Ricerche comparative sulla velocità di sedimentazione delle emazie (VOS) su sangue arterioso evenoso in soggetti malati, Policlinico (sez. prat.) **57**: 349, 1950.
16. Strumia, M. M., and Principato, L.: The Air Turbine Hematocrit for Measurement of the Relative Volume of Packed Red Cells, Am. J. Clin. Path. **20**: 419, 1950.
17. Faergeman, P.: The Normal Values for Hemoglobin, Erythrocytes and Cell Volume Per Cent, and the Corpuscular Constants Derived Thereof, in Children 8-14 Years, Acta med. scandinav. **95**: 566, 1938.
18. Friedman, S., Robie, W. A., and Harris, T. N.: Occurrence of Innocent Adventitious Cardiac Sounds in Childhood, Pediatrics **4**: 782, 1949.
19. McNemer, Q.: Psychological Statistics, New York, 1939, John Wiley & Sons, Inc., p. 66
20. Unpublished data.
21. McNemer, Q.: Psychological Statistics, New York, 1939, John Wiley & Sons, Inc., p. 96.
22. Dixon, W. J., and Massey, F. J.: Introduction to Statistical Analysis, New York, 1951, McGraw-Hill Book Co., p. 108.
23. Power, F. W.: Accuracy and Precision of Microanalytical Determinations of Carbon and Hydrogen, a Statistical Study, Indust. & Engin. Chem. (Analytical Ed.) **11**: 660, 1939.
24. Dixon, W. J., and Massey, F. J.: Introduction to Statistical Analysis, New York, 1951, McGraw-Hill Book Co., Inc., pp. 84-90.
25. McFarlane, R. G., and O'Brien, J. R.: The Rationale of the Blood Sedimentation Rate, Practitioner **157**: 1, 1946.
26. Berg, S.: Unreliability of Oxalated Blood in Determination of Erythrocyte Sedimentation Rate, J. Lab. & Clin. Med. **24**: 757, 1939.
27. Davis, L. J.: The Blood Sedimentation Rate: A Critical Clinical Survey, Practitioner **157**: 13, 1946.
28. Gilmour, D., and Sykes, A. J.: Westergren and Wintrobe Methods of Estimating E.S.R. Compared, Brit. M. J. **2**: 1496, 1951.
29. Jamra, M., Antunes, M. L., and Mendes, F. T.: Estudo Estatìstico E Crìtico Da Hemosedimentaçào Com Os Anticoagulantes Usuais, Antes E Apòs O Almòço E Comparativamente Nos Tubos De Wintrobe E. Westergren, Hospital, Rio de Janerio **37**: 123, 1950.
30. Rosen, M. S.: Extrinsic Factors Influencing the Sedimentation Rate, M. J. Clin. Path. **16**: 681, 1946.
31. Goldberger, E. W.: A Comparative Study of the Erythrocyte Sedimentation Test with the Hellige-Vollmer (Langer) Microsedimeter and Modified Westergren Method, J. Lab. & Clin. Med. **25**: 657, 1940.
32. McKinley, J. B., and Jackson, R. L.: Comparison of Westergren and Kato Erythrocyte Sedimentation Rate Readings. Relation to the Clinical Status of Children With Rheumatic Fever, Am. J. Dis. Child. **67**: 474, 1944.

33. Ström, J.: Mikromethode für die Senkungsreaktion, Acta paediat. **14**: 567, 1932-33.
34. Nichols, R. E.: A Study of Phenomenon of Erythrocyte Sedimentation II. Establishment of Reliable Measurement of Phenomenon—Its Reproducibility and Limitations, J. Lab. & Clin. Med. **27**: 1410, 1942.
35. Nielsen, G.: Heparin and the Blood Sedimentation Reaction, Acta med. scandinav. **3**: 66, 1942.
36. Unpublished data.
37. Kitamura, K.: The Relation Between Erythrocyte Sedimentation Velocity and Age, Race and Blood Type, J. Chosen Med. Assn. **29**: 59, 1939.
38. Westergren, A.: The Technique of the Red Cell Sedimentation Reaction, Am. Rev. Tuberc. **14**: 94, 1926.
39. Osgood, E. E., Baker, R. L., Brownlee, I. E., Osgood, M. W., Ellis, D. M., and Cohen, W.: Total, Differential and Absolute Leukocyte Counts and Sedimentation Rates of Healthy Children Four to Seven Years of Age, Am. J. Dis. Child. **58**: 61, 1939.
40. Osgood, E. E., Baker, R. L., Brownlee, I. E., Osgood, M. W., Ellis, D. M., and Cohen, W.: Total, Differential and Absolute Leukocyte Counts and Sedimentation Rates for Healthy Children. Standards for Children Eight to Fourteen Years of Age, Am. J. Dis. Child. **58**: 282, 1939.
41. Benson, L., and Rogers, E. J.: The Blood Sedimentation Rate in Healthy Girls, J. Lab. & Clin. Med. **26**: 987, 1944.
42. Roche, C. F., Stannus, D. G., and Isberg, E. M.: Erythrocyte Sedimentation Rate Determinations on Normal Youths, J. Lab. & Clin. Med. **28**: 297, 1942.
43. Greisheimer, E. M., Treloar, A. E., and Ryan, M.: The Inter-relation of Cutler, Linzenmeier and Westergren Sedimentation Tests, Am. J. M. Sc. **187**: 213, 1934.
44. Mahoney, E. A., Jr. Worcester, J., and Massell, B. F.: Correlation of Erythrocyte Sedimentation Rates as Determined by the Rourke-Ernstene and by the Wintrobe-Landsberg Method, Am. J. M. Sc. **221**: 402, 1951.
45. Hynes, M., and Whitby, L. E. H.: Correction of the Sedimentation Rate for Anaemia, Lancet **235**: 249, 1938.
46. Gibson, H. J.: Discussion on the Effects of Physical Treatment on the Arneth Count and Sedimentation Rate in Rheumatic Conditions, Proc. Roy. Soc. Med. **31**: 309, 1937.
47. Terry, R.: Erythrocyte Sedimentation in Anaemia, Brit. M. J. **2**: 1296, 1950.
48. Sinton, J. R.: Clinical Value of Some Methods of Estimating Erythrocyte Sedimentation Rate, Brit. M. J. **1**: 391, 1948.
49. Mugrage, E. R., and Andresen, M. I.: Values for Red Blood Cells of Average Infants and Children, Am. J. Dis. Child. **51**: 775, 1936.
50. Mugrage, E. R., and Andresen, M. I.: Red Blood Cell Values in Adolescence, Am. J. Dis. Child. **56**: 997, 1938.
51. Hamre, C. J., and Wong, K. K. L.: Hematologic Values for Normal Children Three, Four and Five Years of Age Living in Hawaii, Am. J. Dis. Child. **60**: 22, 1940.
52. Andresen, M. I., and Mugrage, E. R.: Venous and Peripheral Red Blood Cell Values, Am. J. Clin. Path. **8**: 46, 1938.
53. Faergeman, P.: On the Cause of the Unreliability of Some Hematological Examinations With Special Reference to the Question of Normal Values, Acta med. scandinav. **94**: 429, 1938.
54. Osgood, E. E., and Baker, R. I.: Erythrocyte, Hemoglobin, Cell Volume and Color, Volume and Saturation Index Standards for Normal Children for School Age, Am. J. Dis. Child. **50**: 343, 1935.
55. Hahn, Karlheinz: Personal communication.
56. Levy-Solal, E., Badin, J., and Djazmati, K.: Un nouveau mode d'étude clinique du sang du cordon: la mesure de la vitesse de sédimentation en tube incliné, Gynéc. et obst. **49**: 329, 1950.
57. Morrison, I. R.: Observations on Blood Sedimentation Mechanism, Am. J. Clin. Path. **11**: 578, 1941.
58. Astraldi, D. F.: Il test della velocita disedimentazione delle emazie, Policlinico (sez. prat.) **56**: 1409, 1949.
59. Fuente-Hita, F.: Une nouvelle technique de sédimentation sanguine: L'hémosédimétrie en tube incliné, Ann. Biol. Clinique **5**: 129, 1947.
60. Badin, J.: La sédimentation sanguine en tube incline; intérêt clinique et théorique de ses données et de leur relation avec les données de la sédimentation en tube vertical, Ann. Biol. Clinique **5**: 135, 1947.
61. Badin, J.: Effects de diverses dilutions du sang sur la vitesse de sédimentation globulaire en tube vertical et en tube incliné. Causes des phénomènes observés, Ann. Biol. Clinique **5**: 150, 1947.
62. Josserand, A., and Rendu, G.: Étude comparative des vitesses de sédimentation globulaire observées par les methodes de Westergren et de Cordier-Chaix en ce qui concerne spécialement la sedimentation du première quart d'heure, Lyon med. **183**: 387, 1950.

PARTIAL EVENTRATION OF THE RIGHT DIAPHRAGM

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EVENTRATION of the diaphragm is a relatively rare condition in which a portion of the diaphragm is elevated without loss of continuity of the muscle. The abnormality has been found at all ages. The etiology is not known, but is believed to occur as both a congenital and acquired lesion.[1] Of the sporadic cases reported, the majority have been in adults, and the left hemidiaphragm has been most often involved. Only a few cases of right-sided eventration in children have been reported, and no reference to this condition has been found in the American pediatric literature.

The first case of eventration of the diaphragm was published by Petit[2] in 1774. An occasional report appeared in the literature thereafter, and in the literature and a total of several cases. Reviews by Bayne-Jones,[3] Korns,[4] Reed and Borden,[5] and Nylander and Elfring[6] have summarized the literature and a total of several hundred cases have been presented. Most of those reported were in adults. In 1947 Bisgard[7] was able to find only twelve cases in infants and children. Bisgard's report of a right-sided eventration was the first reported case of successful surgical repair in an infant. Beck and Pixley[8] and State[9] also have reported surgical corrections of eventration in infants. The following case is presented to acquaint pediatricians with the entity, and to emphasize the danger of blind needling of thoracic masses.

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CASE REPORT

F. H., a 5-year-old white male, was admitted to Hahnemann Hospital pediatric ward because of a mass in the mediastinum.

The child was born at home after an uneventful pregnancy, the mother's sixth. Labor and delivery were normal. Birth weight was 8 pounds. There were no physical abnormalities noted during the neonatal period. Formula feeding was initiated and he vomited constantly during the first several weeks. At the age of 9 weeks he was admitted to another hospital for study of recurrent vomiting. A diagnosis of pylorospasm was made. During investigation, x-ray study of the chest revealed a mass in the right hemithorax of unknown nature. Fluoroscopic reports stated that the mass appeared to be independent of the diaphragm. The boy was discharged on thickened feedings and seemed to do well. Growth and development appeared to progress normally. He sat at 7 months, walked at 12 months, and talked at 18 months. During the first year he had frequent upper respiratory infections and fevers of unknown origin. Cyanosis on crying was noted. At 11 months he had a fever followed by several convulsions, and he was admitted to a hospital for study. Chest x-ray at this time again revealed a mass, and the mother was told that the child had a "dermoid cyst" of the chest. She was instructed that surgery would be necessary at a later date. From the age of one year until the present the boy has had frequent attacks of "bronchitis" and "colds."

About two weeks prior to admission, the patient was seen by a physician for treatment of an upper respiratory infection. Because of the history of mediastinal mass, the physician suggested admission to the hospital. The child was admitted to another hospital where a diagnosis of mediastinal tumor was made. The boy was then transferred to Hahnemann Hospital for surgery.

Parents and seven siblings are in good health. No history of neurological or respiratory difficulties and no history of tuberculosis or allergy were found.

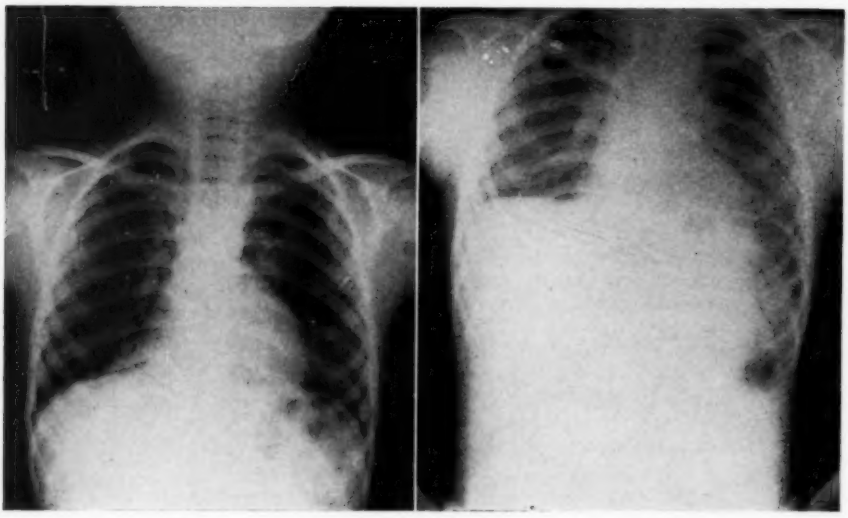
On physical examination the child was found to be a thin, pale white child who did not appear acutely ill. He seemed somewhat delayed mentally. The head was asymmetrical with flattenir ; of the occipital portion. The tympanic membranes were thickened. Examination of the eyes revealed no abnormalities. Nose and throat were normal; the tonsils were not enlarged. On the right side of the neck a small branchial cleft cyst was noted. No enlarged cervical nodes were palpated. Trachea was in the midline. Chest examination revealed a depression of the anterior wall and lower left side of the chest. The xiphoid protruded prominently. A normal percussion note was elicited over the entire chest. Breath sounds were normal; no râles were heard. No abnormality of costal margin motion was noted. The heart was not enlarged. There was a normal sinus rhythm. Sounds were of good quality. A soft systolic murmur was heard. This was loudest in the depressed area of the chest just to the left of the sternum. The liver was palpable 2 cm. below the costal margin. The spleen and kidneys were not felt. No clubbing of fingers was noted. No cyanosis, even on crying, was detected. The femoral pulsations were forceful.

Laboratory studies revealed red blood count 4,700,000; hemoglobin 12.0 grams; white blood count 9,100; mature polymorphonuclears 68 per cent; stab forms 3 per cent; lymphocytes 27 per cent; monocytes 26 per cent. Urinalysis: Sp. Gr., 1.024; color, yellow; reaction, acid; a trace of acetone was noted. An occasional white cell and squamous cell were noted in microscopic examination. Bleeding time was two minutes. Coagulation time was 6 minutes 30 seconds. Blood type O,Rh positive.

X-ray and fluoroscopy showed a smooth ovoid mas of homogeneous density approximately 4.5 cm. in diameter in the right cardiophrenic sulcus. It was inseparable from the right atrial margin of the cardiac silhouette. The subjacent portion of the diaphragm was intact and moved with normal amplitude of excursion. The mass did not pulsate. There was no displacement of the esophagus.

A tentative diagnosis of pericardial cyst or teratoma was made. It was then decided that an exploratory thoracotomy should be performed rather than diagnostic needling of the mass. The child was operated upon by Dr. Charles P. Bailey. Under cyclopropane anesthesia with endotracheal intubation, exploration of the right chest was performed. In the region close to the pericardial edge, a bulge 4 x 5 cm. was noted. The diaphragm appeared to be continuous over the mass. An incision was made over the surface of the tumor, and the diaphragm overlying the mass was found to be a fibrotic layer. The mass beneath the diaphragm appeared to be normal liver tissue. There were adhesions between the liver and the diaphragm. A biopsy was taken from the mass, and the fibrotic diaphragm was imbricated so that it overlapped 5 cm. on its own surface. This produced a more normal contour of the diaphragm. Postoperative course was completely uneventful and the child was discharged nine days postoperative.

X-ray examination following surgery revealed the right lung to be completely re-expanded. No evidence of postoperative inflammation was found (Fig. 1). Follow-up examinations three and one-half months postopera-



A. *B.*

Fig. 1.—*A*, Preoperative posteroanterior view of chest. Mass in right cardiophrenic angle approximately 4 x 5 cm. in diameter. *B*, Postoperative view of chest showing obliteration of the mass following surgery.

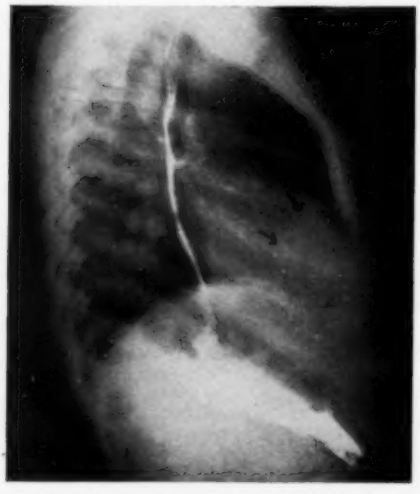


Fig. 2.—Lateral view of the chest (preoperative). The anterior position of the mass (arrows) is clearly seen.

tive show that the child has been well since discharge from the hospital. His appetite has improved, and there has been a slight gain in weight.

COMMENT

Fluoroscopy and multiple roentgenographic studies were interpreted as revealing a nonpulsating, smooth ovoid tumefaction in the right cardiophrenic angle. The diaphragms were reported as showing normal movement. The question of diagnostic thoracentesis of the tumor mass was considered, but it was felt that needling of an unknown mass was a potentially dangerous and unnecessary procedure. Regardless of what type of lesion would be found, surgery would still be necessary. Exploratory thoracotomy under modern conditions presents a minimal risk, and the dangers of pneumothorax, pneumomediastinum, and hemorrhage are averted. Unsuspected puncture of the liver in such a case could easily cause fatal hemorrhage into the peritoneal cavity.

Diagnostic pneumothorax and pneumoperitoneum have been done in efforts to differentiate eventration from diaphragmatic hernia.[6, 7, 10] While these procedures are undoubtedly useful in the differential diagnosis, it is our feeling that surgical exploration presents less risk and permits definitive repair at the same time. Surgery in this instance represents a more conservative approach to diagnosis and treatment.

Several explanations as to the etiology of eventration have been advanced. In 1935 Reed and Borden[5] reviewed the literature, and in eighty-three cases, thirty patients were under the age of 25. This suggested that many of the cases were of congenital origin. The cases presented by Whitmore and Kahlstrom[11] (age: 1 year) and Bisgard[7] (age: 6 weeks) support this theory. Our case, with x-ray evidence of a mass at the age of 2 months, probably fits into the category of congenital abnormality. Other suggested causes have been inflammation and trauma. Nylander and Elfring[6] in 1951 presented several cases in which a previous history of pleurisy was obtained and suggested that the inflammation may weaken the diaphragm and cause relaxation.

Many patients with eventration of the diaphragm are asymptomatic, and the lesion is discovered during the examination for other conditions. In adults the symptoms vary greatly, depending on the site of the lesion and the extent of involvement. Among the symptoms mentioned have been dyspnea, cyanosis, gastrointestinal upset, cardiac disturbances, and generalized malaise. In infants, if the lesion is severe enough to cause difficulties, the picture is one of respiratory embarrassment. Dyspnea, cyanosis, and frequent respiratory infection are seen. Our patient had a history of gastrointestinal difficulty at birth. A story of cyanosis during crying was also elicited. Previous reports have emphasized the almost constant finding of a positive Hoover or Korm's sign. This is an increased excursion of the costal margin on the affected side, and it is thought to be due to the uninhibited action of the intercostal muscles. It was not noted in this case. Other physical signs are inconstant, and depend upon the extent of the lesion.

In asymptomatic cases where the diagnosis is established by roentgen study, probably no treatment is neces-

sary. Where symptoms exist, exploratory thoracotomy is a safe procedure. The most successful procedure has been a plication of the diaphragm which replaces the abdominal contents and permits re-expansion of the lungs.

SUMMARY

A case of partial eventration of the right diaphragm in a child has been presented. The dangers of blind diagnostic aspiration have been reviewed. It is suggested that exploratory thoracotomy be done in preference to aspiration, pneumothorax, or pneumoperitoneum.

REFERENCES

1. Bergmann, J.: Ueber Relaxatio diaphragmatica: Ergeben d. inn. Med. u Kinderh. **12**: 327, 1913.
2. Petit, J. L.: Traité des maladies chirurgicales et des operations qui leur conviennent, Paris, 1774, T.-F. Didot, vol. 2, p. 226.
3. Bayne-Jones, S.: Eventration of the Diaphragm With Report of a Case of Right-Sided Eventration, Arch. Int. Med. **17**: 221, 1916.
4. Korns, H. M.: The Diagnosis of "Eventration" of the Diaphragm, Arch. Int. Med. **28**: 192, 1921.
5. Reed, J. A., and Borden, D. L.: Eventration of the Diaphragm With Report of Two Cases, Arch. Surg. **31**: 30, 1935.
6. Nylander, P. E., and Elfring, G.: Partial Eventration of the Diaphragm, Ann. Chir. et Gyn. Fenn. **40**: 1, 1951.
7. Bisgard, J. D.: Congenital Eventration of the Diaphragm, J. Thoracic Surg. **16**: 4841, 1947.
8. Beck, W. C., and Pixley, C.: Eventration in the Child. Case Successfully Treated Surgically, Guthrie Clin. Bull. **19**: 151, 1950.
9. State, D.: The Surgical Correction of Congenital Eventration of the Diaphragm, Surgery **25**: 461, 1949.
10. Faulkner, W. B.: Diaphragmatic Hernia and Eventration. Use of Pneumothorax in Differentiation, Am. J. Roentgenol. **45**: 72, 1941.
11. Whitmore, O. S., and Kahlstrom: Eventration of Right Diaphragm, New York State J. Med. **42**: 1587, 1942.

EISENMENGER'S COMPLEX IN ASSOCIATION WITH CONGENITAL TRICUSPID ENDOCARDITIS (FETAL)

REVIEW OF LITERATURE AND REPORT OF CASE

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EISENMENGER[9] in a lengthy report described the clinicopathological findings in a 32-year-old male whose cause of death was attributed to congestive heart failure. He made the correct ante-mortem diagnosis of congenital heart disease associated with interventricular septal defect.

Abbott[3, 4] designated the name Eisenmenger's complex to a group of eight cases in which she recorded the basic anomalies to consist of high interventricular septal defect, dextroposition of the aortic valve overriding the septal defect associated with clinical manifestations of cyanosis, dyspnea, enlargement of the heart, diastolic murmurs, clubbing, and polycythemia.

The embryological basis for Eisenmenger's complex was ably documented by Abbott.[3, 4] The dynamics[13] and physiological studies were carried out by Bing and associates[6, 7] and Cournand and co-workers[8] by cardiac catheterization.

To date eighteen cases of Eisenmenger's complex with pathological study have been reported. Among some of these the following associated abnormalities were recorded: Abbott[1, 2] illustrated the associated abnormality of aneurysm of cusps of the aortic valve. Abbott[3, 4] and Rosedale[24] reported a patent interatrial septal defect; Abbott[3, 4] and Talley and Fowler,[27] hypoplasia of the aorta; Baumgartner and Abbott[5] and Saphir and Lev,[25] an anomalous coronary artery; Taussig and Semans,[28] retraction and insufficiency of the right aortic cusps, and Saphir and Lev,[25] coarctation of the aorta.

The following case report is of an Eisenmenger's complex with its two basic defects in the heart: high interventricular septal defect, dextroposition of the aortic valve overriding the septal defect, with associated abnormalities of "fetal endocarditis" of the tricuspid valve, dilatation of the pulmonary artery and hypertrophy and dilatation of the right ventricle. This is the first such case reported in the literature so far as we could ascertain.

CASE REPORT

W. M., a 4-month-old male infant, was hospitalized because of irritability, restlessness, and crying for twelve hours. At delivery his weight was 3 pounds, 4 ounces. He was discharged thirty-five days following delivery, weighing 5 pounds.

The family history was irrelevant.

Physical Examination.—He was well nourished and well developed, and in moderate distress. The temperature was elevated. The pulse was rapid, regular, and of fair quality. The cardia was enlarged; diastolic mur-

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murs were elicited at the apex and pulmonic areas. There was cyanosis. Suggestive pneumonitis associated with areas of atelectasis in the right upper and lower lobes was noted. The extremities were normal. The genitals were normal.

Course.—The infant continued to have intermittent attacks of cyanosis and dyspnea, and the temperature was spiking between 102.4° and 103.8° F. In spite of massive antibiotic therapy of penicillin, streptomycin, aureomycin, ACTH, he went downhill and died after two months' hospitalization.

Laboratory Data.—There was a polycythemia; urine was negative; Kahn test was negative. Roentgen films of the chest revealed focal bullous emphysema, atelectasis, and pneumonitis in the right upper and lower segments of the lung. The transverse diameter of the heart was enlarged (Fig. 1).

Autopsy Findings.—He measured 23 inches in length and weighed 13 pounds. The scalp, face, neck, chest, genitals, and extremities were normal. The thymus was coarsely lobulated and weighed 8.5 grams. The thyroid gland weighed 3.0 grams.

The heart was unusually large, globular in shape, weighed 115 grams, and measured 6.2 cm. across the base and 5.8 cm. from base to the rounded apex, made up of both right and left ventricles. The epicardium was pale, glistening, and translucent. The right atrium and ventricle were dilated and the hypertrophied myocardium measured 0.6 cm. in thickness. The edematous tricuspid valve measured 4.0 cm. The free border of the atrial surface was lined by a row of raised, translucent, pale gray at-

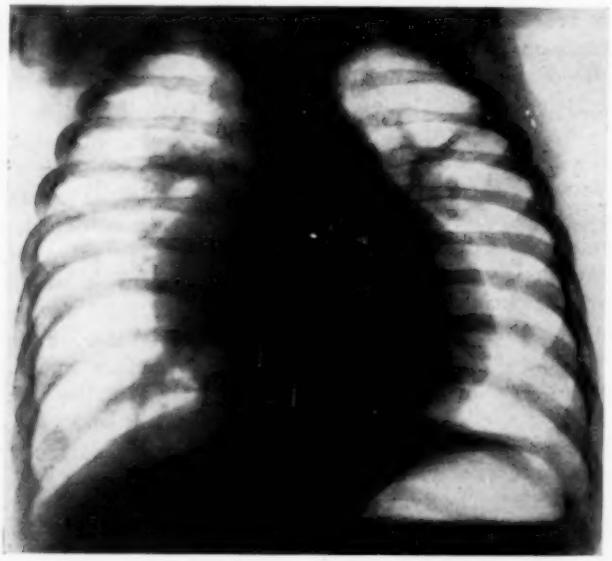

Fig. 1.—Transverse enlargement of the heart with marked prominence of the pulmonary artery and secondary branches.

tached vegetations, pin point in size, extending to the endocardium of the chordae tendineae. The firm tricuspid leaflet partly overhung the high interventricular septal defect, an example of congenital endocarditis (exaggerated by protrusion through the ventricular defect during ventricular systole). The pulmonary valve measured 3.5 cm. Dilatation of main pulmonary arteries and branches was noted. The foramen ovale was patent. The left atrium and ventricle were dilated and hypertrophied, measuring 1.2 cm. in thickness. The mitral valve measured 3.8 cm. The ventricular surface showed the high interventricular septal defect measuring 0.8 cm. The aortic orifice measured 2.8 cm.; the valvular dextroposition overrides the septal defect. The ductus arteriosus was obliterated. The arch of the aorta was dilated. The coronary arteries were normal. (Figs. 2, 3, 4, 5.)

The combined weight of the lungs was 380 grams. There was pneumonitis, edema, and congestion. Increased fibrosis and vascular intimal and medial hypertrophy were noted.

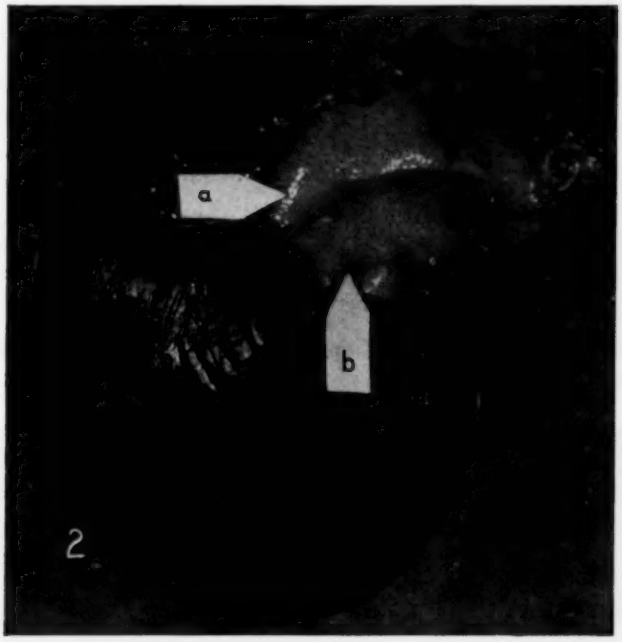

Fig. 2.—Globular, transverse enlargement of the heart. *a*, Dextroposition of aorta. *b*, Dilatation of pulmonary artery.

The spleen weighed 38 grams. Fibrous markings and congestion were dominant. The pancreas and adrenals were normal. The liver weighed 230 grams. Congestion was dominant. The kidneys weighed 38 grams each. Fetal lobulation and congestion were noted. The gastrointestinal tract, urinary bladder, prostate, and testicles were normal. The brain

Fig. 3.—*c*, High interventricular septal defect. *d*, Hypertrophy and dilatation of the right and left ventricles. *e*, Dextroposition of aortic valve overriding the septal defect.

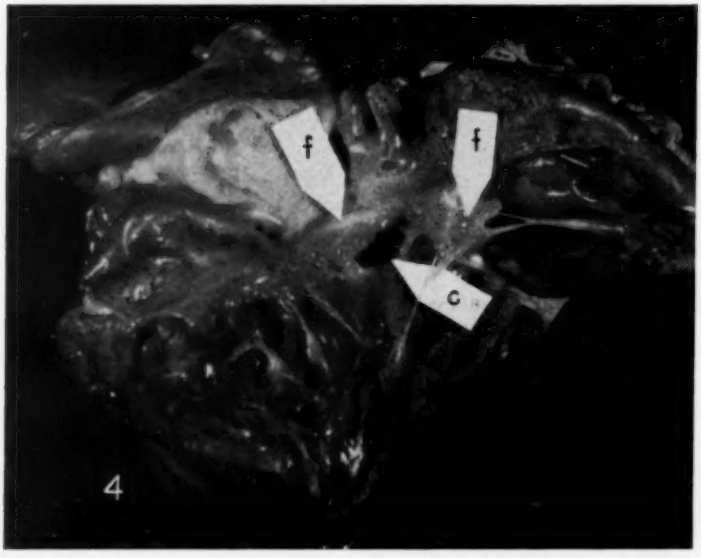

Fig. 4.—*f*, Congenital tricuspid verrucous endocarditis (fetal) overhanging (*c*) the high septal defect.

weighed 65 grams. Cerebral edema and congestion were noted.

Final Diagnosis.—Eisenmenger's complex: high interventricular septal defect; dextroposition of the aortic valve overriding the septal defect; endocarditis, verrucous, nonbacterial, of the tricuspid valve (fetal), congenital; dilatation of the pulmonary artery; hypertrophy and dilatation of the right ventricle; splenomegaly, congestive, severe; interstitial pulmonary fibrosis, bilateral; pneumonitis; pulmonary atelectasis; focal emphysema, bullous; umbilical hernia; congestion of viscera.

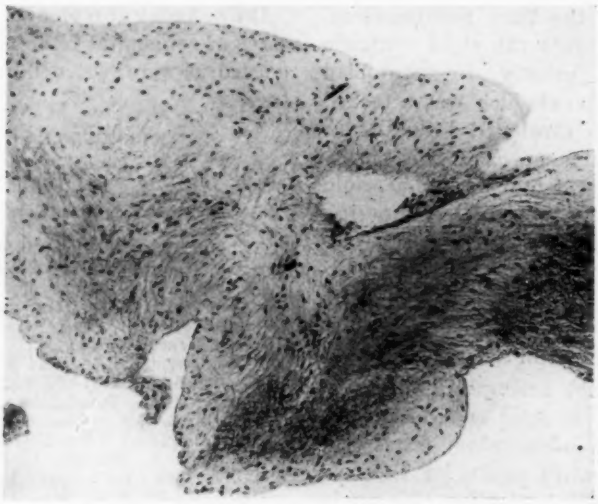

Fig. 5.—Endocarditis, nonbacterial, of tricuspid valve showing spindle and round-cell proliferation.

DISCUSSION

Rokitansky[23] in introducing the term fetal endocarditis considered the lesion to be inflammatory and the basic mechanism of cardiac anomalies. Vierordt's[30] and Garrod's[12] hereditary and familial concept of congenital heart lesion was based on demonstrating identical cardiac malformations in two sisters and four brothers. This concept was supported by the valuable contribution of the developmental study by Harris[15] of a miscarried fetus. Monckenberg's[21] personally contributed cases of cardiac anomalies, in addition to those he collected in reviewing the literature, totaled thirteen examples. This inspired Nagel,[22] Kockel,[17] Ganeff,[11] Fisher,[10] LeTulle,[18] and Loeser[19] to the contribution of cardiac malformation case reports, still nursing the idea of inflammation as the causative mechanism for valvular stenoses. Keith,[16] in his investigation of 270 cases, came to the monumental conclusion that the lesions so far on record considered to be of inflammatory genesis were of developmental origin, basing his conclusion on the concomitant anomalies he found in other parts of the body during fetal development.

Thomson[29] reported a case of fetal endocarditis in a male infant dying at 2½ years of age as a result of congenital tricuspid insufficiency terminating in cardiac insufficiency. Gutzeit[14] reported the cause of death of a 26-year-old female due to congenital tricuspid insufficiency resulting from fetal endocarditis associated with hypertrophy and dilatation of the right ventricle and dilatation of the right pulmonary artery. McIntosh[20] reported a case of fetal endocarditis in which two small defects lay just anterior to the pars membranacea, one opening into the right ventricle through a greatly hypertrophied chorda tendinea which was attached to the much shortened infundibular tricuspid valve segment. The findings were accidental in a 44-year-old female dying of postoperative peritonitis. Stohr[26] reported a case of tricuspid valvular endocarditis in a newborn infant. The anatomic and histological observation was considered to be of primary fetal inflammation.

We are not attempting to revive the interest in fetal endocarditis on the basis of inflammatory genesis, or as the causative agent for the congenital cardiac anomalies. We are in full agreement with the concept established by Abbott[3, 4] of errors in developmental processes as the basis of cardiac anomalies. A case is presented in which congenital tricuspid valvular verrucous endocarditis (fetal) was demonstrated in association with Eisenmenger's complex. Four cases appear to be on record in which tricuspid valvular endocarditis (fetal) was demonstrated and clinically interpreted as congenital tricuspid insufficiency terminating in myocardial insufficiency and congestive failure.

SUMMARY

An additional example of a case of Eisenmenger's complex with pathological study is illustrated and described.

To date eighteen such cases with pathological study were recorded.

The first documented case of Eisenmenger's complex in association with congenital verrucous tricuspid endocarditis (fetal) is presented.

An additional example of congenital tricuspid endocarditis is presented.

Only four previously described cases of congenital fetal tricuspid endocarditis were recorded in the literature.

REFERENCES

1. Abbott, M. E.: Nelson's New Loose Leaf Medicine, New York **4**: 265, 1920.
2. Abbott, M. E.: Ann. Clin. Med. **4**: 189, 1925-1926.
3. Abbott, M. E.: Osler's Modern Medicine, Philadelphia and New York, 1927, Lea & Febiger.
4. Abbott, M. E.: Atlas of Congenital Cardiac Disease, New York, 1936, American Heart Association.
5. Baumgartner, E. A., and Abbott, M. E.: Am. J. M. Sc. **177**: 639, 1929.
6. Bing, R. J., Handelsman, J. C., and Campbell, J. A.: Mod. Concepts Cardiovascular Dis. **17**: No. 3, 1948.
7. Bing, F. J., Vandam, L. D., and Gray, F. D., Jr.: Bull. Johns Hopkins Hosp. **80**: 323, 1947.
8. Cournand, A., Baldwin, J. S., and Himmelstein, A.: New York, 1949, The Commonwealth Fund.
9. Eisenmenger, V.: Ztschr. f. klin. Med. (supp.) **32**: 1, 1897.
10. Fisher, B.: Frankfort Ztschr. f. Path. **7**: 83, 1911.
11. Ganeff, M.: Dissert. Wurzburg, 1910.
12. Garrod, A. E.: Tr. Clin. Soc. London **32**: 6, 1899.
13. Goldberg, H., Silber, E. N., Gordon, A., and Katz, L. N.: Circulation **4**: 343, 1951.
14. Gutzeit, A.: Virchows Arch. **137**: 353, 1922.
15. Harris, H. A.: J. Anat. **56**: 76, 1923.
16. Keith, A.: Lancet **2**: 1272, 1924.
17. Kockel, R.: Verhandl. d. Gesellsch. deutsch. Naturf. u. Aerzte, Köln **80**: 39, 1908.
18. LeTulle: Presse méd. **22**: 436, 1914.

19. Loeser, A.: Virchows Arch. f. path. Anat. **219**: 309, 1915.
20. McIntosh, C. A.: Ann. Clin. Med. **4**: 748, 1926.
21. Monckenberg, J. G.: Verhandl. d. deutsch. Gesellsch. **11**: 224, 1908.
22. Nagel, W.: Dissert., Freiburg, 1908.
23. Rokitansky: Defekte der Scheidewande des Herzens, Vienna, 1875.
24. Rosedale, R. S.: Am. J. Path. **11**: 333, 1935.
25. Saphir, O., and Lev, M.: Am. Heart J. **21**: 31, 1941.
26. Stohr, G.: Arch. Path. **17**: 311, 1934.
27. Talley, J. E., and Fowler, K.: Am. J. M. Sc. **191**: 618, 1936.
28. Taussig, H. B., and Semans, J. H.: Bull. Johns Hopkins Hosp. **66**: 156, 1940.
29. Thomson, J.: Edin. Hosp. Rep. **2**: 292, 1894.
30. Vierordt: Specielle Pathologie und Therapie, Vienna, 1898, A. Holder.

A COMPARISON OF EGRESSIN AND GENTIAN VIOLET IN THE TREATMENT OF ENTEROBIASIS (PINWORM INFESTATION)

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IN THE search for more effective therapeutic agents for enterobiasis, Egressin* (3-methyl-6-isopropylphenyl ester of N-isoamylcarbamic acid) was obtained from Germany. Eichholtz and Hotovy,[1] and Sauer and Weissflug[2] had reported excellent clinical results and a low incidence of toxic reactions from the use of this drug.

Toxicity studies[3] in this country in which large doses (0.2 to 1.0 Gm. per kilogram per day) were administered to dogs for periods of as long as thirty-two days indicated that no or negligible toxicity should be anticipated from the clinical use of Egressin.

Goddard and Brown[4] were the first to use Egressin clinically in this country. They employed the dosage schedule of the German clinicians, consisting of three doses per day, each of 2 Gm. of the drug for two days in the treatment of older children and adults, and 1 Gm. per dose, three times a day for two days, for children of 2 to 12 years of age. A purge of magnesium sulfate was given on the following day. N.I.H. swabs were made to check the effect of the medication. The results were not encouraging since in only fifteen of twenty-nine patients did it appear that the parasites had been eliminated. These authors suggested that larger doses or more prolonged administration might increase the effectiveness of Egressin. Relatively small amounts of alcohol taken during or shortly after a course of Egressin were followed by cramps, lightheadedness, flushing, and pounding in the head.

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*The Egressin used in this study was furnished by Sharp & Dohme.

MATERIALS AND METHODS

Infants and children suspected of having enterobiasis on the basis of suggestive symptoms or of the mothers' reports of having seen worms were examined and treated in the outpatient department of St. Christopher's Hospital for Children. The relative efficacy of Egressin and gentian violet was evaluated from the observations of 126 treatments given to infants, children, and adults.

The scotch tape method of securing material for microscopic examination was demonstrated to the mothers in the clinic. A 5-inch strip of scotch tape was placed sticky side out over the end of a wooden tongue depressor.[5] The space between the index finger and thumb of a clenched fist simulating the anal orifice proved convenient in showing how the sticky surface of the tape should be pressed into the anal folds. The mother was asked to purchase a fresh roll of ¾ inch scotch tape and was given a tongue depressor for each member of the family.

Cooperating mothers obtained a specimen from each member of the family immediately after they arose on three mornings. It was emphasized that this should be done before

the individuals went to the bathroom or dressed. After the strip of tape had been pressed against the anus it was folded so that the adhesive sides opposed one another, and the free ends were attached to a label on which the name of the person and the date were written. These specimens were mailed in a sealed envelope or were brought to the clinic; they were examined within a week of their collection. Although the larvae in the ova died within a few days, the ova were easily recognizable for months after the preparations had been made.

Early in the course of the study the mothers were requested to examine the children's anal areas one or two hours after they had gone to bed. In a number of infected children, mothers saw worms emerge from the anal orifice after the buttocks had been spread apart for a few minutes when the child was in a prone position under a strong light.

In the clinic, strips of scotch tape were pressed against the labia minora and inner surfaces of the labia majora in little girls with vaginitis. Ova of pinworms were often demonstrated by this technique. Mothers were asked not to repeat this diagnostic method.

When epithelial cells, vegetable cells, or meat fibers were not seen on preparations on which no ova could be demonstrated in the pretreatment phase, the preparations were discarded as being unsatisfactory. The mothers who had made them were reinstructed in the method, and new slides were obtained.

I examined all of the preparations. Each scotch tape strip was placed sticky side down on a glass slide, and the impression made by the anal orifice was visualized by looking through the slide toward a bright light. Red pencil lines drawn on either side of this impression directed the observer's attention during the microscopic examination. The tape was then partially peeled from the slide, one or two drops of toluene (or xylene) were placed on the slide, and the tape replaced.[6] The toluene cleared the preparation of most artefacts and facilitated visualization of the ova. After systematic search for ova under the low-power objective, the slide was classified as positive or negative.

Each mother was given a mimeographed list of directions. The use of alcohol and tobacco was prohibited during medication with Egressin. A low fat diet was also advised because this chemical is more soluble in oil or fat than in water. Since many mothers inquired about hygienic measures designed to prevent reinfection and cross-infection, appropriate instructions were given.* All members of each family in which there were children with enterobiasis were treated, and the dose for each was included in the written directions.

Initially Egressin was tested in doses calculated according to body weight (0.045 Gm. per pound of body weight per day). The compound was administered without laxatives. After each three-day period of treatment a cleansing enema was given. The entire treatment was repeated after twelve days.

Dosage Schedule of Egressin: Study I

Body Weight in Pounds	*Prescribed as Follows*
10	½ small (0.25 Gm.) tablet t.i.d. pc for 3 days.

*Since hygienic measures of themselves have been demonstrated to have little or no value,[11] their use was not considered therapeutically significant.

20	1 small (0.25 Gm.) tablet t.i.d. pc for 3 days.
30	1½ small (0.25 Gm.) tablets t.i.d. pc for 3 days.
40	2 small (0.25 Gm.) tablets t.i.d. pc for 3 days.
50	3 small (0.25 Gm.) tablets t.i.d. pc for 3 days.
60	3 small (0.25 Gm.) tablets t.i.d. pc for 3 days.
70	2 large (0.50 Gm.) tablets t.i.d. pc for 3 days.
80	2½ large (0.50 Gm.) tablets t.i.d. pc for 3 days.
90	2½ large (0.50 Gm.) tablets t.i.d. pc for 3 days.
100	3 large (0.50 Gm.) tablets t.i.d. pc for 3 days.
120	3½ large (0.50 Gm.) tablets t.i.d. pc for 3 days.
130 and over	4 large (0.50 Gm.) tablets t.i.d. pc for 3 days.

When it became apparent that this treatment schedule was not very effective, a second therapeutic regimen was started. With doses calculated according to body weight it was noted that there were more minor toxic symptoms in the older children and adults but more treatment failures in the younger individuals. Accordingly, calculation of dosage on the basis of body surface area was tried in order to increase the dose for smaller children and decrease it for older individuals. No therapeutic measures other than Egressin were used during this second phase of the study. Treatment was administered for five days.

Dosage Schedule of Egressin: Study II

Body Weight in Pounds	*Prescribed as Follows*
Under 10	½ small tablet (0.25 Gm.) t.i.d. pc for 5 days.
10	1 small tablet (0.25 Gm.) t.i.d. pc for 5 days.
20	1½ small tablets (0.25 Gm.) t.i.d. pc for 5 days.
30	2 small tablets (0.25 Gm.) t.i.d. pc for 5 days.
40	3 small tablets (0.25 Gm.) t.i.d. pc for 5 days.
50	3½ small tablets (0.25 Gm.) t.i.d. pc for 5 days.
60	2 large tablets (0.5 Gm.) t.i.d. pc for 5 days.
70 — 90	2½ large tablets (0.5 Gm.) t.i.d. pc for 5 days.
100 — 130	3 large tablets (0.5 Gm.) t.i.d. pc for 5 days.
140 and over	3½ large tablets (0.5 Gm.) t.i.d. pc for 5 days.

To test whether the standards employed to evaluate the efficiency of Egressin were reasonable, therapeutic trials with gentian violet were carried out to provide a basis for comparison. Gentian violet was administered for five days (Study III) and seven days (Study IV), respectively.[10] Tablets with a four-hour enteric coating were taken after meals.

Dosage Schedules of Gentian Violet: Studies III and IV

Age in Years	*Total Daily Dose (Given in Three Divided Doses After Meals)*
Under 4	1 or 2 0.010 Gm. capsules
4 - 6	3 0.010 Gm. capsules
6 - 8	6 0.010 Gm. capsules
8 - 13	3 0.030 Gm. capsules
Adults	6 0.030 Gm. capsules

When one therapeutic attempt failed, the same individual was included in the same or another study. The interval between treatments was at least one month, so that it seems improbable that the second therapeutic effort was augmented by any action of the first.

RESULTS AND DISCUSSION

The scotch tape slides were more accurate for detection of parasites than were the mothers' reports of observing worms. Many unsuspected cases were revealed by the laboratory method. Conversely, in one instance a mother and older child thought they saw worms during a period when twenty-one slides were examined without demonstrating ova. Another mother brought in a "worm" which under the microscope proved to be a

thread. When there was a difference of opinion between mother and physician, the mother was invited to bring the worms preserved in alcohol, or to continue making slides.

consecutive negative slides within one month after completion of treatment. According to Sawitz and Karpinos seven N.I.H. swabs are necessary to detect 99 per cent* of the infected cases in a given population.[7] Since the

TABLE I. STUDY I: RESULTS OF TWO THREE-DAY COURSES OF THERAPY WITH EGRESSIN (ENEMA GIVEN AFTER EACH COURSE)

PATIENT	SEX	AGE (YR.)	PRETREATMENT POSITIVE/TOTAL SLIDES	RESULTS	TOXICITY
1. R. F.	F	2	1/1	Failure	None
2. D. F.	M	4	1/1	Failure	None
3. T. F.	M	6	1/1	Cure	None
4. Jos. O.	M	7	2/2	Failure	Vomiting
5. John O.	M	9	1/1	Failure	None
6. F. O.	M	10	1/1	Cure	None
7. James O.	M	11	1/1	Failure	None
8. E. R.	F	21	1/1	Cure	Vomiting
9. D. F.	F	27	1/1	Cure	None

TABLE II. STUDY II: RESULTS OF A FIVE-DAY COURSE OF THERAPY WITH EGRESSIN (WITHOUT ENEMAS)

PATIENT	SEX	AGE (YR.)	PRETREATMENT POSITIVE/TOTAL SLIDES	RESULTS	TOXICITY
1. R. F.[a]	F	2	3/3	Cure	None
2. J. A. R.	F	2	4/4	Failure	None
3. R. F.[b]	F	2	1/1	Doubtful	None
4. M. H.	F	2	2/3	Failure	None
5. C. R.	M	2	1/3	Failure	None
6. J. R.	F	4	5/6	Failure	None
7. T. B.	M	5	1/3	Failure	None
8. G. S.	M	5	2/3	Cure	None
9. J. H.	M	5	2/3	Failure	None
10. W. B.	M	6	3/3	Failure	None
11. E. H.	M	6	3/3	Failure	None
12. W. R.	M	8	1/3	Failure	Abdominal pain and tenesmus
13. W. R.[c]	M	8	2/3	Failure	Abdominal cramps
14. M. R.	F	8	3/3	Cure	None
15. S. A. H.[d]	F	9	2/3	Cure	Mild abdominal pain
16. H. F. H.	F	12	1/6	Cure	Abdominal cramps
17. J. H.[e]	M	12	2/3	Doubtful	None
18. S. B.	F	31	3/3	Cure	Fatigue
19. H. H.	F	36	2/3	Cure	None

[a]Previous Egressin treatment failure.

[b]Also Case 1. Treated five months later because of reappearance of worms. Classified as doubtful satisfactory result because positive slide was made the day after treatment, and the next six slides were negative.

[c]Also Case 12—retreated one month later.

[d]Previous Egressin treatment failure.

[e]Classified as doubtful satisfactory result because of five negative slides.

For the purpose of evaluation of the four therapeutic regimens the following definitions were adopted.

An *infected individual*—at least one positive scotch tape slide.

A *cured individual*—one proved to be infected, and who had at least seven

newer scotch tape method has proved to be more effective than other methods,[8, 9] it would appear that this

*If the probability of obtaining a positive N.I.H. swab in an infected individual with a single N.I.H. test is 50 per cent, 99 per cent of the infected individuals in a population will be discovered by the examination of seven N.I.H. swabs.

requirement for a cure, although not absolute, was reasonably rigid.

Treatment failure—when one or more ova are found within a month after medication.

Doubtful cases—individuals who had had five or six negative slides following treatment, or only one positive slide on the day immediately following completion of therapy.

Reinfection was assumed to have occurred if ova were found in a previously cured individual more than a month after treatment. If one accepts the life cycle of *Enterobius vermicularis* to be four to seven

TABLE III. STUDY III: RESULTS OF A FIVE-DAY COURSE OF THERAPY WITH GENTIAN VIOLET (WITHOUT ENEMAS)

PATIENT	SEX	AGE	PRETREATMENT POSITIVE/TOTAL SLIDES	RESULTS	TOXICITY
1. M. H.	F	2	2/3	Failure	None
2. C. R.[a]	M	2	2/3	Cure	None
3. M. H.[b]	F	2	1/3	Cure	None
4. W. K.	M	4	3/3	Failure	None
5. J. R.[c]	F	4	3/3	Failure	None
6. M. A. C.	F	4	3/3	Failure	None
7. E. H.	M	4	2/3	Cure	None
8. J. C.	M	6	1/3	Cure	None
9. S. S.	F	7	1/3	Failure	None
10. R. K.	M	8	2/3	Cure	None
11. J. K.	M	10	2/3	Cure	None
12. P. K.	M	11	3/3	Cure	None
13. R. K.	F	32	2/3	Cure	None

[a]Previous Egressin treatment failure.
[b]Case 1—retreated one month later.
[c]Previous Egressin treatment failure.

TABLE IV. STUDY IV: RESULTS OF A SEVEN-DAY COURSE OF THERAPY WITH GENTIAN VIOLET (WITHOUT ENEMAS)

PATIENT	SEX	AGE	PRETREATMENT POSITIVE/TOTAL SLIDES	RESULTS	TOXICITY
1. R. F.	F	3	3/3	Failure	None
2. R. A. S.	F	3	2/3	Cure	None
3. D. H.	F	4	4/4	Cure	None
4. H. J.	M	4	1/3	Cure	None
5. R. K.	M	4	3/3	Failure	None
6. D. S.	M	4	3/3	Cure	None
7. B. H.	F	5	3/4	Cure	None
8. M. S.[a]	F	5	6/6	Cure	None
9. B. S.[b]	F	6	6/6	Cure	None
10. P. J.	M	7	1/3	Cure	Stomach-ache
11. J. M.[c]	M	7	2/3	Doubtful	Abdominal pain
12. G. I.	F	8	1/5	Cure	None
13. R. S.	M	9	1/3	Cure	Vomiting
14. D. J.	F	9	1/3	Cure	Headache
15. G. M.	F	9	3/3	Cure	Vomiting
16. R. H.	M	10	4/4	Cure	None
17. C. K.	M	11	3/3	Cure	None
18. J. H.	M	13	4/4	Cure	None
19. P. H.	M	15	2/4	Cure	None
20. M. A. M.	F	15	3/3	Cure	Vomiting
21. C. H.	M	16	3/4	Cure	None
22. G. F.	F	24	2/3	Cure	None
23. F. H.	F	42	1/4	Cure	None

[a]Previous treatment failure after administration of gentian violet for five days.
[b]Previous treatment failure after administration of gentian violet for five days.
[c]Classified as doubtful result because of only six negative slides.

weeks,[11] ova swallowed on the day following successful therapy could mature and reproduce a month later.

Even with two courses of treatment including cleansing enemas, Egressin "cured" less than one-half of the patients in Study I (Table I). With a five-day course of this compound (Study II) the results were no better (Table II).

Toxic reactions consisting of vomiting, dizziness, abdominal cramps, and diarrhea occurred in twenty of sixty-two persons treated with Egressin. Almost all of these reactions were so mild that treatment was not interrupted. Because patients apparently heeded the mimeographed instructions warning against the use of alcoholic beverages or any liquid medicine (elixirs and extracts), no instances of an "Antabuse-like" reaction were reported. Smoking did not seem to produce untoward reactions during the period of treatment.

Gentian violet given for a five-day period (Study III) cured eight out of a group of thirteen patients. Although more than one-half of the patients treated were cured, a comparison with the results obtained with Egressin are not statistically significant. (P greater than 0.50.)

Although repeated eight-day courses of gentian violet are usually considered necessary for optimal results,[12] it was found that one seven-day regimen cured twenty of twenty-two patients. Treatment IV gave results highly significantly better than the other three treatments (P = 0.01 – 0.001).

In the gentian violet groups, headache, nausea, vomiting, abdominal pain and cramps occurred in fourteen of sixty-four treatments.

The results of the four regimens are compared in Table V.

TABLE V

TREATMENT SCHEDULE	NUMBER CURES	NUMBER FAILURES	DOUBTFUL	TOTAL NUMBER TREATED	TOTAL NUMBER WITH ANY TOXICITY
I. Two 3-day courses of Egressin with enemas	4 (44%)	5 (56%)	0	15	6 (40%)
II. One 5-day course of Egressin without enemas	7 (41%)	10 (59%)	2	47	14 (30%)
III. One 5-day course of gentian violet without enemas	8 (62%)	5 (38%)	0	28	4 (14%)
IV. One 7-day course of gentian violet without enemas	20 (91%)	2 (9%)	1	36	10 (28%)

SUMMARY AND CONCLUSIONS

1. Various dosage schedules of Egressin and gentian violet were compared in the treatment of patients with enterobiasis.

2. Egressin therapy for six days (given in two divided courses twelve days apart, each course followed by an enema) and a five-day course were no more effective than a five-day treatment with gentian violet.

3. Gentian violet given for seven days proved very successful.

The statistical evaluation of these studies was done by Mr. Joseph L. Ciminera, Biometrician, Research Division, Sharp & Dohme, Inc.

I am indebted to Drs. Paul C. Beaver and Rodney C. Jung (Department of Tropical Medicine and Public Health, School of Medicine, Tulane University and Charity Hospital, New Orleans) for advice and guidance. They very kindly showed me the results of their work comparing Egressin, Diphenan, gentian violet, and nightly enemas for the treatment of enterobiasis.[13]

REFERENCES

1. Eichholtz, F., and Hotovy, R.: Ueber die Pharmakologie und Toxikologie des Egressin, Schweiz. med. Wchnschr. **80**: 732, 1950.
2. Sauer, A., and Weissflug, I.: Klinische Pruffing des Egressin, Schweiz. med. Wchnschr. **80**: 737, 1950.
3. Beyer, K. H.: Personal communication.
4. Goddard, R. F., and Brown, H. W.: The Treatment of Pinworm Infection (Enterobius vermicularis) with Egressin, J. PEDIAT. **40**: 469, 1952.
5. Jacobs, A. H.: Enterobiasis in Children; Incidence, Symptomatology, and Diagnosis, With Simplified Scotch Cellulose Tape Technique, J. PEDIAT. **21**: 497, 1942.
6. Beaver, P. C.: Methods of Pinworm Diagnosis, Am. J. Trop. Med. **29**: 577, 1949.
7. Sawitz, W., and Karpinos, B. D.: Statistical Problems Involved in Application of N.I.H. Swab for Diagnosis of Oxyuriasis, Am. J. Hyg. **35**: 15, 1942.
8. Mazzotti, L., and Osorio, Maria Teresa: Diagnosis of Enterobiasis; Comparative Study of Graham and Hall Techniques in Diagnosis of Enterobiasis, J. Lab. & Clin. Med. **30**: 1046, 1945.
9. Jeffery, G. M.: Incidence of Enterobius Vermicularis in Puerto Rican Children, With Comparison of Two Diagnostic Methods, J. Parasitol. **36**: 485, 1950.
10. Beaver, P. C., and Jung, R. C.: Diagnosis and Treatment of Pinworm Infection (Enterobiasis), Bull. Tulane Med. Faculty **9**: 44, 1950.
11. Belding, D. L.: Textbook of Clinical Parasitology, New York 1952, Appleton-Century-Crofts, Inc.
12. Faust, E. C.: In Mitchell-Nelson Textbook of Pediatrics, W. E. Nelson, ed. Philadelphia, 1950, W. B. Saunders Co.
13. Jung, R. C., and Beaver, P. C.: Treatment of Pinworm Infection (Enterobiasis) With Diphenan, Egressin and Gentian Violet, Pediatrics (in press).

OBSERVATIONS OVER A FIVE-YEAR PERIOD OF A PATIENT WITH NEPHRITIS TREATED WITH SEVENTY-NINE INFUSIONS OF 10 PER CENT GELATIN SOLUTION

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EDEMA occurring as a complication during nephrosis or during the nephrotic stage of nephritis is not uncommon. At times this complication becomes the primary concern in the treatment. It is practically always associated with a decreased serum protein and serum albumin. A few cases of edema with normal serum protein values have been reported, and in these situations an electrolytic imbalance, as well as the presence of an antidiuretic substance produced by the kidney, has been suggested as the causative factors. However, these exceptions are infrequent. Usually edema is associated with decreased serum protein and decreased serum albumin. The treatment has generally included the following measures: salt restriction, elimination of secondary infections, and the judicious use of digitalis. Sometimes ascites requires aspiration. In cases where these measures failed to reduce the edema, procedures to restore the osmotic tension of the blood have been tried. The substances used have been (1) low salt albumin, (2) low salt plasma, (3) low salt globulin, and (4) salt-free 10 per cent gelatin solution.

The purpose of this paper is to report our results with the use of a 10 per cent gelatin solution in the treatment of a patient with severe nephrosis when edema had become the main complication. We were surprised by the absence of untoward effects either immediate or delayed. Three other patients were treated in similar fashion and similar results were observed. None of the others had as many infusions or were observed over such an extended period. Gelatin infusions caused dramatic diuresis in nephritis when the serum proteins were decreased.

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METHOD

The gelatin solution consisted of 45 Gm. of gelatin dissolved in 450 c.c. of distilled water. Just prior to use, the temperature of the solution was brought to 36° C. and 50 c.c. of a 50 per cent glucose in distilled water was added.

The low-salt albumin solution consisted of 25 Gm. of dried albumin to which was added 250 c.c. of distilled water.

Both solutions were administered intravenously and total urinary output and body weight were recorded daily. Before the initial use of either solution, a period of observation was allowed to determine which way the natural course of the disease was taking. We did not administer either solution when the disease was entering a stage of spontaneous remission.

CASE REPORT

First admission: Oct. 22, 1947, to Nov. 6, 1947.

The patient was an 8-year-old white boy admitted because of marked generalized edema extending from the lower extremities to face and involving abdomen and scrotum. The development of the edema had been gradual and had first been noted by his parents about five months previous. Swelling of the eyelids occurring in the morning had been the first sign.

His past history had been uneventful except for "asthmatic" attacks which occasionally occurred during the summer but never required medical attention. He had suffered from repeated attacks of sore throat and tonsillitis and at times had been treated with sulfa drugs. Physical examination revealed: temperature 99.4° F., pulse 112, respiration 20, blood pressure 124/60. Generalized anasarca was present involving eyes, extremities, and trunk. Tonsils were hypertrophic and edematous. Heart sounds were clear, no murmurs were noted. Lungs were clear to percussion and auscultation. Ascites was rather marked and moderate distension of abdomen was present. No liver or spleen was palpated.

Laboratory data were as follows: Urine: Sp. gr. 10.38, occasional granular cast, albumin 4 plus. Sugar was negative. Microscopic: 3 to 4 white blood cells, no red blood cells. Kahn test was negative. Complete blood count: red blood count 4,200,000, white blood count 6,550, hemoglobin 13.4 grams; polymorphonuclears 62, lymphocytes 32, eosinophils 4, monocytes 2. Nonprotein nitrogen 78 mg. per cent. Total serum protein: 3.65 grams; albumin 2.08, globulin 1.57.

Chest x-ray showed increased density of the right lower lobe which was interpreted to be bronchopneumonia.

Course during first hospitalization:

The patient was placed on a low-salt, high-protein diet. Penicillin 50,000 U. was given every three hours for four days. Plasma 2,500 c.c. was given on the fifth day. Pneumococcus polysaccharide 1 c.c. was given on the sixth day and repeated on the seventh day.

He was discharged from the hospital on the fourteenth day. The edema had not decreased. The urinary output was less than 200 c.c. per day and the condition was considered terminal.

Table I shows daily weight and urinary output during the first hospital stay in evidence of the progressive downward trend which the patient manifested.

TABLE I. DAILY URINE OUTPUT AND DAILY WEIGHT

DATE	URINE OUTPUT (C.C.)	WEIGHT (LB.)
First hospital stay		
1947		
Oct. 23	450	
24	550	
25	500	
26	600	77½
27	850	
28		78
29	150	
30	650	82½
31	800	78½
Nov. 1	280	
2		
3	200	78¾
4	50	
5	50	
6	?	79½

Second admission: Nov. 12, 1947, to March 13, 1948.

Six days after discharge the patient was readmitted in critical condition. The generalized edema had increased and both eyes were closed. The abdomen was extremely distended, the skin over the extremities was stretched and glossy in appearance. The child was unable to move by himself and any motion of the bed caused severe pain. Daily weight determinations could not be taken till the sixth hospital day because of the severity of his complaints. At that time he had lost considerable edema. His weight was 80 pounds on the sixth day. Upon admission his temperature was 101.8° F., pulse 104, respiration 32. Blood pressure could not be taken because of severe edema of arm.

Laboratory data were as follows: red blood count 3,200,000, white blood

count 12,000, hemoglobin 9.6 grams, polymorphonuclears 82 per cent, lymphocytes 16 per cent, monocytes 2 per cent, hematocrit 24. Total serum protein 3.5 grams; albumin 1.54 grams, globulin 1.96 grams.

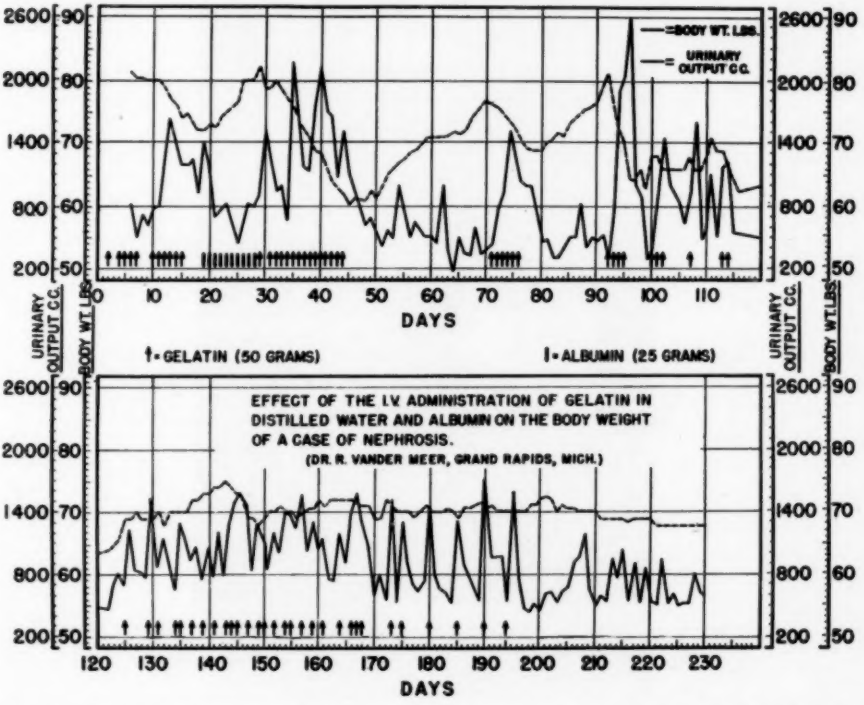
His hospital course was as follows:

The patient was placed on a low-sodium, high-protein diet. He received infusions of low-salt albumin and 10 per cent gelatin solution. The administration of gelatin infusions was interrupted several times because the material was not always available. The interruptions are designated as control periods although actually there was no choice in the matter.

Fig. 1 shows the daily weight and urinary output over a period of 230 days. From the seventy-sixth to the ninety-second day, gelatin was not available and the patient gained, 68 to 82 pounds. After daily infusions of gelatin from the ninety-second to the ninety-fifth day he lost 18 pounds of edema weight.

During the interval between the second and third hospital admissions, serum protein determinations were done on the following dates:

July 8, 1948: Total serum protein 7.23, albumin 2.162 grams, globulin 3.61 grams.


=BODY WT. LBS.
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URINARY OUTPUT C.C.
BODY WT. LBS.
DAYS
†-GELATIN (50 GRAMS)
I-ALBUMIN (25 GRAMS)
EFFECT OF THE I.V. ADMINISTRATION OF GELATIN IN DISTILLED WATER AND ALBUMIN ON THE BODY WEIGHT OF A CASE OF NEPHROSIS.
(DR. R. VANDER MEER, GRAND RAPIDS, MICH.)

Fig. 1.—Second admission. Correlation of body weight, daily urinary output with albumin and plasma infusions over a period of 230 days.

July 14, 1948: Total serum protein 6.23, albumin 3.7 grams, globulin 2.57 grams.

His albumin loss continued and varied from 885 mg. per twenty-four hours on July 8, 1948, to 1,690 mg. per twenty-four hours on Sept. 23, 1948.

The patient was kept on a low-salt,

high-protein diet and was well enough to return to school.

Third admission: July 4, 1949, to July 27, 1949.

The patient was readmitted the next year, July 4, 1949, because of recurrence of symptoms. He had contracted mumps on June 15, 1949. Edema and oliguria had developed during this attack.

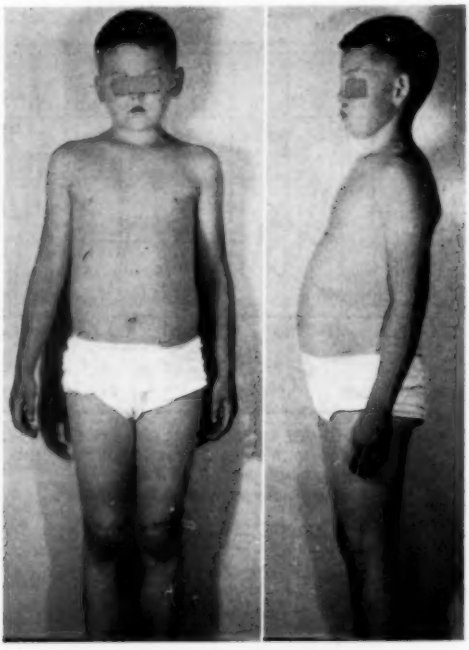

Fig. 2. Fig. 3.

Figs. 2 and 3.—Patient on July 7, 1949, weighing 91¼ pounds.

Admission examination showed: temperature 99.8° F., pulse 100, respiration 28, weight 90½ pounds. Skin was very edematous and there was marked ascites. The lungs showed moist râles and some dullness was noted in the left base.

Laboratory work revealed red blood count 5,070,000, white blood count 6,450, hemoglobin 15.5 grams, polymorphonuclears 50, lymphocytes 46, monocytes 3, eosinophils 1. Total serum protein 4.6 grams, albumin .67 gram, globulin 3.93 grams.

During his hospital stay, the usual treatment was given and he received daily infusions of 500 c.c. of 10 per cent gelatin solution. He lost 18 pounds of body weight during the first seven days. Figs. 2 and 3 were taken on July 7, 1949, when the patient weighed 91¼ pounds. Figs. 4 and 5 were taken seven days later when he weighed 73¼ pounds.

Fourth admission: Aug. 25, 1949, to Sept. 8, 1949.

The patient was readmitted Aug. 25, 1949. During the intervening forty-eight days at home he had been kept at complete bed rest. The low-sodium diet was enforced. He had not received any gelatin. Upon discharge from the third hospital stay, the total serum protein was 3.89 grams. Almost

immediately upon discontinuing the gelatin infusions the weight increased and the urinary output decreased. He gained 21 pounds during the forty-eight days at home. He was readmitted with a total body weight of 94 pounds and urinary output of less than 50 c.c. daily. His condition upon admission was considered critical. Daily infusions of gelatin were again started and after nine days his body weight was 71 pounds. He had lost 23 pounds of edema fluid and his urinary output averaged 1,750 c.c. daily.

Physical examination shows a normal-appearing 13-year-old boy, 5 feet 4 inches tall, weighing 105 pounds. There was no evidence of peripheral edema.

Laboratory studies include the following: complete blood count: red blood count 4,810,000, white blood count 5,400, hemoglobin 12.8 grams, polymorphonuclears 43, lymphocytes 38, monocytes 8, eosinophils 10, basophil 1. Sedimentation rate was 14. Total serum protein 6.7 grams, albumin 4.5 grams, globulin 2.2 grams.

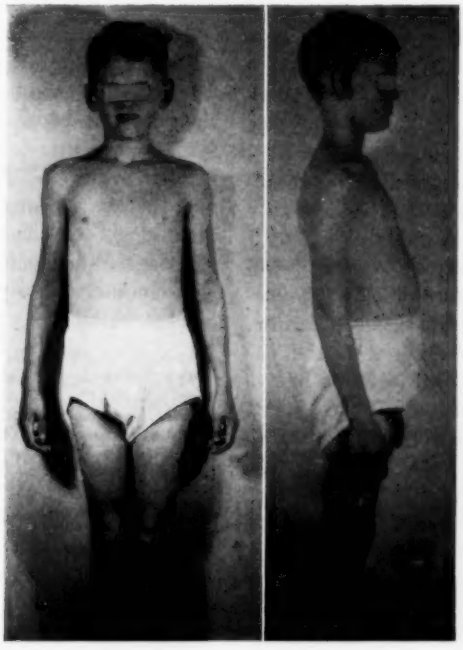

Fig. 4. Fig. 5.

Figs. 4 and 5.—Patient seven days later, July 14, weighing 73¼ pounds after daily infusion of 10 per cent gelatin solution.

Fifth observation:

Patient was seen at the office on Nov. 4, 1952, during a routine check-up. He has no complaints. He is allowed full activity, goes to school and handles a "paper route" on the side. His diet has been restricted as to salt intake. Total urinary protein loss was 0.06 gram for a twenty-four-hour period.

DISCUSSION

The comparative value of gelatin and low-salt albumin in the treatment of edema occurring in Bright's disease

were reviewed by Thorn and Tyler in 1947.[1] Their results showed a more favorable response with albumin than gelatin. Our observations were the exact opposite.

There are many different gelatins. The size and shape of the molecule are the most important variants. The gelatin used in our case had a mean molecular weight of 45,000.

Other workers have described untoward reactions to gelatin infusion. Abdominal pain, vomiting, and anorexia have been mentioned as some of the milder ones. Much attention has been directed to "gelatin nephrosis." Skinsnes[2] demonstrated this lesion in twenty-three autopsies. His patient had received infusions of 800 c.c. of 8 per cent gelatin solution. The epithelial cells of the proximal convoluted tubules showed a granular variolated swelling, often so severe that the tubular lumen was almost closed. Sometimes the affected cells seemed necrotic. These changes were noted if the patient received gelatin 120 hours before death. None were noted if the patient received no gelatin during the last 120 hours of life. All his patients were surgical, and presumably started out with normal kidneys. Gelatin was usually given to combat shock. It may be unwise to assume that similar changes occur when gelatin is given in a nephrotic kidney as in the kidney of a patient in shock.

Other investigators[3] have demonstrated the retention of gelatin in the reticuloendothelial cells of lymph nodes as well as granular retention in liver cells. Many of these changes may be temporary in nature. It is often difficult to correlate clinical observations with pathological findings. The fact that our patient received seventy-nine injections of 45 Gm. of gelatin in a 10 per cent solution over a period of twenty-two months, without untoward reactions as noticed over a five-year period, makes one feel that liver and kidney damage as shown by the pathological picture were reversible.

CONCLUSION

Over a period of twenty-two months we treated edema occurring in a patient with nephrosis with a total of seventy-nine infusions of a 10 per cent gelatin solution. The diuretic effect and the loss of total body weight was definitely established. No untoward reactions either immediate or delayed were noticed over a period of five years of observation.

Gelatin was supplied by the Upjohn Company, Kalamazoo, Michigan. Albumin was supplied by the American Red Cross, National Research Council. Grateful acknowledgment is made of the interest and aid furnished by the house staff and the laboratory personnel at St. Mary's Hospital.

REFERENCES

1. Thorn, George W., and Tyler, Frank H.: Clinical Management of Edema in Bright's Disease, M. Clin. North America **31**: 1077, 1947.
2. Skinsnes, O. K.: Gelatin Nephrosis: Renal Tissue Changes in Man Resulting From the Intravenous Administration of Gelatin, Surg., Gynec. & Obst. **85**: 563, 1947.
3. Hartman, Frank W.: Fate and Disposal of Plasma Substitutes, Ann. New York Acad. Sc. **55**: 504, 1952.

TETANUS NEONATORUM

Review of Twenty-Six Cases

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INFECTIONS of the umbilical stump were once extremely common, but have diminished in number with the introduction of aseptic obstetrical techniques. However, the practice of midwifery in some rural areas of the South, and such unhygienic customs as placing dung or soot on the umbilical stump, still are responsible for an alarming number of infections yearly. This report reviewing twenty-six cases of tetanus neonatorum which were seen at the Charity Hospital, New Orleans, between 1946 and 1951 is presented to emphasize the continuing importance of the infection.

The mere fact that *Clostridium tetani* is present does not necessarily mean that tetanus will develop; local conditions in the wound must be suitable. The organisms will proliferate only in the presence of an oxidation-reduction potential far lower than that existing in normal living tissue. Such a fall in potential may occur as a result of the presence in the wound of necrotic tissue, of soil, of bits of cloth, metal, or wood, or of tentanus toxin. Once the organism begins to grow, it produces toxin, and thereafter can maintain the conditions necessary for continued multiplication. If conditions for growth are not optimal, tetanus spores may persist in the tissues for many months in a viable but dormant state.

Tetanus bacilli show little capacity to invade, and are in themselves harmless. They cause disease by virtue of a soluble exotoxin elaborated in the course of growth. Actually, two toxins are produced, tetanolysin and tetanospasmin. Tetanolysin has a lytic effect on red blood cells in vitro, but has not been shown to contribute to the production of symptoms in man. Tetanospasmin is a protein substance with potent neurotoxic properties, which acts at two points in the body; on the neuromuscular end organs, causing sustained muscle spasm, and on the motor nerve cells of the spinal cord, medulla, and pons, causing convulsive seizures. Tetanospasmin has a strong affinity for nerve tissue of susceptible animals and, when once combined with it in vivo, cannot be neutralized by any amount of antitoxin. The means by which toxin travels from the local lesion to the nervous system is still a matter of controversy. However, recent evidence makes it seem probable that the toxin is absorbed by the lymphatics, carried into the circulation, and distributed to the central nervous system by the arterial blood supply.[1]

Tetanus neonatorum carries an extremely high mortality rate which varies inversely with the length of

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incubation period. The most common portal of entry is the umbilical stump, although circumcisions have been incriminated.

The onset of the disease is usually characterized by inability to nurse followed by generalized tonicity, opisthotonus and generalized convulsions; "risus sardonicus" is typically present. The cause of death in these patients is generally unknown, but respiratory arrest due either to the tetanus toxin or to the heavy sedation characteristically used seems to be frequent in the early stages of the disease. Deaths occurring later seem to be associated more commonly with secondary infection or inanition. Among serious complications bronchopneumonia and compression fractures of the lumbar vertebrae are most frequent.

The frequency with which tetanus neonatorum was being encountered stimulated us to review the experiences of others. Vinnard[2] reported eleven patients with tetanus neonatorum treated at the Charity Hospital, New Orleans, from November, 1934, to November, 1944. It was disturbing to find that we were encountering a greater incidence and higher mortality than had been reported previously from the same hospital. In contrast to the cases reported by Vinnard over a ten-year period our series of twenty-six patients was accumulated in six and one-half years between November 1, 1944, and June 1, 1951. There were six recoveries and twenty deaths, resulting in a mortality rate of 77 per cent. The number of males and females was about equal, but there were four Negro infants for each white. During the same period the ratio of Negro to white admissions was approximately 2 to 1. Fifteen of the twenty-six patients were delivered by midwives, one by a physician at home, one by cesarean section in another hospital, one by the grandmother, and one by the mother alone. No information was available in the remaining cases.

Eighteen infants presented grossly infected umbilical stumps at the time of admission. Of this number only one recovered. In five cases the umbilical stumps appeared normal; of this group, three infants recovered. There was no report of the condition of the cord in three cases. Positive cultures for *Cl. tetani* were obtained in only three cases.

The average age at onset of symptoms was 6.1 days in those patients who died (range 4 to 9 days) while it was 8 days in those who recovered (range 6 to 9 days).

A further analysis of our data for periods of highest incidence did not reveal a significant seasonal variation.

The method of treatment of the twenty-six cases varied considerably. Patients who were in the hospital one day or less before death either received inadequate therapy or died before benefit from treatment could be evaluated. For the sake of clarity, clinical management is considered in five categories: (1) antitoxin, (2) sedation, (3) antibiotics, (4) surgery, and (5) nutrition and fluids. The order of discussion does not indicate relative importance, and quantitative considerations except in the case of antitoxin will not be discussed because of extreme variations.

The amount of antitoxin given varied from 35,000 to 190,000 units and was given intramuscularly, intravenously, and locally around the umbilicus or by any combination of

these three routes. Patients who recovered did not receive any more antitoxin on the average than those who died, nor did the method of administration appear to affect the outcome. One infant recovered after receiving only 35,000 units intramuscularly while one recovered after receiving 190,000 units. The usual dosage given approximated 100,000 units but no particular preference for a specific method of administration could be determined.

In attempting to attain adequate sedation various drugs were tried. These included phenobarbital, chloral hydrate, paraldehyde, Avertin, Tolserol, and combinations of one or more of these agents. Chloral hydrate, used frequently in the first two years of the study period, is rarely employed at present. It may be of some significance that all survivors received phenobarbital, three of these receiving no other sedative. In our hospital Avertin was first used in the treatment of tetanus neonatorum in 1949. Only two patients in our series have received this drug. The difficulties attendant upon its rectal administration are deterring factors in the case of the young infant, but are not necessarily prohibitive. Further use of this drug is warranted.

The efficacy of antibotic administration in tetanus is controversial except in connection with prevention of secondary infection. In our series all patients but three were given penicillin. Of the six infants who recovered five received varying amounts of the drug, up to 50,000 units every six hours. One survivor did not receive the drug but had survived without therapy of any kind for twelve days before coming to the hospital. The administration of additional antibiotics such as streptomycin, Chloromycetin, aureomycin, and sulfadiazine to occasional patients did not appear to influence the course of the disease.

Surgical treatment was limited to the performance of tracheotomies, and umbilectomies. The latter procedure was performed on four infants during the years 1945 and 1946, and from 1949 to 1951 seven cases received tracheotomy. In no cases were both operations performed on the same individual. It is interesting that the six patients who recovered received no surgery of any kind. However, since tracheotomy is a formidable procedure in young infants it constituted a final resort in critically ill patients of this series and can hardly be correlated with survival.

The administration of fluids and maintenance of electrolyte balance are vital factors in management. The difficulties encountered in fluid administration are numerous, but of various techniques used, intubation was most frequently chosen as a means of maintaining adequate intake. As evidence of the importance placed on alimentation, almost all patients received oral glucose or formula during the first days of observed illness.

DISCUSSION

A great predominance of Negro patients was encountered even considering the fact that there were only twice as many Negro as white admissions during the period covered by the study. Obviously the socioeconomic status of the Negro particularly in rural areas is of prime importance in evaluating the apparent racial predominance. Only one infant among the patients reported

was born in a hospital. Eighteen of the twenty-six infants were delivered by midwives, a vast majority of whom can be presumed to have had little formal training in their work. Complex problems in public education, training of professional personnel, and distribution of medical services must be solved before tetanus neonatorum can be eliminated.

Although the presence of a grossly infected umbilicus seemed to correlate with a more serious prognosis, many of the fatal infections had short incubation periods and therefore less time for apparent healing of the umbilical stump. There was a definite relation between length of incubation period and prognosis. An average incubation period of eight days was found among patients who recovered as compared to six days in fatal infections. It is of interest to note that only one infant whose incubation period was less than seven days recovered, and, on the contrary, that only one infant whose incubation period was over seven days died. Our observations indicate that this critical seven-day interval is a valid basis for prognostication regardless of therapy employed.

Surgical débridement was performed for only four cases, all of which terminated fatally. It is of some interest that umbilectomy was performed on the only fatal case having an incubation period of longer than seven days. The value of penicillin could not be assessed since all but three patients received the drug and opportunity for extensive bacteriologic studies was not available. Further, the difficulties of culturing the organisms, even under ideal conditions, are well known. In eight cases having positive cultures for *Cl. tetani* among a large group of older patients who received penicillin, Diaz-Rivera and associates[3] found that five became negative within twenty-four hours, six within forty-eight hours, and seven after twenty-two hours. One patient continued to have positive cultures for twenty-nine days and cleared only after antibiotic therapy to the wound.

Although it is difficult to interpret our data relative to the dosage of antitoxin, large quantities did not prevent death, and recovery occurred in one infant receiving as little as 35,000 units. This might suggest that exuberant dosages are not necessarily advantageous; however, the work of Cooke and Jones[4] suggests that protective titers of antitoxin are more constantly maintained when large doses are given.

Edema of the face and feet was noticed in at least two of the infants ten to fourteen days after admission. Jelliffe[5] reported the same finding in one of his cases. This phenomenon was not satisfactorily explained, but hypoproteinemia or increased sodium intake in the presence of decreased renal function would seem to be the most likely explanations.

At first glance a comparison of 77 per cent mortality in the present series and 55 per cent for the eleven cases reported by Vinnard is most disconcerting. Since all patients with tetanus were admitted to the surgical service during the period covered by the last-mentioned report it was thought that surgical treatment of the primary site of infection might be the determining factor. As already indicated, this was not the case. The possibility that supportive care avail-

able in a quiet, well-staffed emergency observation ward favorably influenced the outcome is suspected but is hard to substantiate. Of great importance in explaining the discrepancy in mortality figures is the fact that the incubation periods in Vinnard's cases varied from eight to twelve days, whereas in the more recent experience at Charity Hospital incubation periods were four to nine days. This further established the seventh day as a crucial time in determining prognosis, and also probably indicates that diagnosis is being made earlier at present and that fewer patients with tetanus are dying before admission to the hospital.

Tetanus antitoxin remains the only specific therapeutic tool at our disposal, and since a primary focus in an infant probably produces at least as much toxin as a similar wound in an adult, the dosage of antitoxin should not be a function of the size or age of the patient. In spite of previously described wide variations in antitoxin dosage among our patients, it is our opinion that following appropriate skin testing, 50,000 units given intravenously and 50,000 units intramuscularly are adequate. Before leaving consideration of immunity, both active and passive acquired immunity should be mentioned. In severe infections even though recovery occurs, antibody formation may be sufficiently depressed to prevent development of protective natural immunity. This was demonstrated by Dudley[6] in 1928. In a more recent paper Cooke and Jones felt that antibody production was not inhibited, but rather that an amount of toxin sufficient to produce clinical symptoms might not be an adequate antigenic stimulus. In any event toxoid should be given these patients during convalescence, and routine immunizations should not be neglected.

An ideal sedative for use in tetanus neonatorum would combine maximal sedative and relaxant effect with minimal respiratory depression. It would be safe for use over long periods, with little cumulative action and would be easy to administer without stimulating the patient. Unfortunately no single drug satisfies all these requirements, and as a consequence a combination of several is usually necessary. Amytal, Seconal, phenobarbital, Avertin, chloral hydrate, paraldehyde, magnesium sulfate, and ether in oil have all been used with variable results. Recently the use of Mephenesin has received considerable attention. Biehl and Helm[7] reported on the intravenous use of the drug in six adults. Relief of trismus, muscular rigidity, and opisthotonus, with little associated sedative effect and no inhibition of the cough reflex was considered striking. On the contrary, severe convulsions were not controlled except when barbiturates were given to the point of narcosis. Significantly these authors could not demonstrate improved mortality rates from the use of Mephenesin.* Santemma and Graham[8] found the effect of Tolserol* lasted only forty-five minutes and also concluded that oral administration of the drug was ineffective. The six infants in this study who received Tolserol were given liberal quantities of the drug, but by the oral route. All died. In spite of serious technical difficulties the use of Tolserol, intra-

*Trade names for 3-ortho-toloxy-1,2-propanediol.

venously, warrants careful trial in tetanus neonatorum.

Curare and its derivatives have been tried, but because of the danger of respiratory paralysis are probably contraindicated.[9] The preparation and administration of Avertin repeatedly to small infants is difficult. In our experience proctitis and associated diarrheal symptoms are frequently complications of prolonged use. Hepatic damage has been reported.

We feel that phenobarbital in doses of 15 to 30 mg. by gavage tube is the most satisfactory over-all sedative. Not infrequently the drug should be injected intramuscularly or intravenously for more rapid action. Cumulative effects from repeated dosage and attendant oversedation must be borne in mind and avoided. In the immediate control of generalized convulsions intravenous Seconal is particularly useful. However, Avertin or paraldehyde rectally can also be used with good effect.

The maintenance of adequate nutrition and fluid intake for two or more weeks in an infant who is continuously and heavily sedated is the greatest single problem in therapy. Probably gastric intubation with a polyethylene catheter of small external diameter, but relatively large lumen, is the best way of giving both fluids and formula.[10] Care must be taken to avoid overdistending the stomach with resulting vomiting and aspiration. Following each gavage feeding of milk the tube must be flushed out with a small amount of distilled water. A constant drip into the gavage tube can be arranged and in selected instances has definite advantages. During the first critical days of the clinical course it is frequently desirable to depend entirely on the intravenous infusion of glucose solutions, electrolytes, and blood or plasma.

Penicillin should be given in doses of 100,000 units every twelve hours for probable in vivo effect on the *Cl. tetani*, and also in an effort to control secondary infection. Other antibiotic or chemotherapeutic agents are employed as indicated to control specific secondary invaders.

The risk of performing surgery on a critically ill infant is great. In addition the benefits derived from umbilectomy are questionable. Therefore the procedure is not recommended. Tracheotomy has a place in the management of individual patients, but should never be performed as a matter of routine. We resorted to the procedure in this group of small infants whenever obstruction of the airway due to laryngeal spasm, inability to swallow, or aspiration could not be handled by other means.

Finally no single factor is more important in caring for the infant with tetanus neonatorum than the constant attendance of a highly skilled nurse. The patient should be placed in an incubator with high oxygen content, and in a dark quiet room since the slightest stimulation may provoke severe rigors. Nursing care must be individualized and the possible benefit of each procedure carefully balanced against the disadvantages of stimulating the infant in any way.

SUMMARY AND CONCLUSIONS

From an experience with twenty-six cases of tetanus neonatorum at Charity Hospital, New Orleans, between 1946 and 1951, it is clear that recovery correlates more closely with

the length of incubation period than with the type of clinical management. Prognosis is relatively good if onset is after the seventh day of life, but is extremely poor if symptoms appear earlier. A single liberal dose of antitoxin (100,000 units) is adequate. Subsequent to recovery the patient should receive toxoid for active immunization. Surgical débridement of the umbilical stump in our experience is not indicated. Maintenance of fluid and electrolyte balance is crucial. Carefully controlled administration of food, fluid, and, in so far as possible, medication through a polyethylene gavage tube is recommended. Although several drugs may be required for adequate sedation, phenobarbital orally, intramuscularly or intravenously is the most useful single agent. Penicillin should be given, and other antibiotics added as indicated for secondary infection. Continuous, highly skilled, and completely individualized nursing care is the most important aspect of therapy. Finally the provision of universally adequate obstetrical care would promptly eliminate tetanus neonatorum.

REFERENCES

1. Harrison, T. R.: Principles of Internal Medicine, ed. 1, Philadelphia, 1950, The Blakiston Co., pp. 892-896.
2. Vinnard, R. T.: 352 Cases of Tetanus, Surgery **18:** 482, 1945.
3. Diaz-Rivera, R. S., Ramirez, E., Pons, E. R., and Torregrosa, M. V.: Management of Tetanus: Effect of Penicillin, J. A. M. A. **147:** 1635, 1951.
4. Cooke, J. V., and Jones, F. G.: The Duration of Passive Tetanus Immunity, J. A. M. A. **121:** 1201, 1943.
5. Jelliffe, D. B.: Tetanus Neonatorum, Arch. Dis. Child. **25:** 190, 1950.
6. Dudley, S.: Quart. J. Med. **22:** 321, 1929.
7. Biehl, J. P., and Helm, R. A.: The Use of Mephenesin in Controlling the Spasms of Tetanus, J. Lab. & Clin. Med. **38:** 791, 1951.
8. Santemma, E. E., and Graham, G. C.: Tolserol in Tetanus, New York State M. J. **50:** 2731, 1950.
9. Greech, O., Woodall, J. P., and Ochsner, A.: The Necessity of Tracheotomy in the Treatment of Tetanus to Prevent Lethal Respiratory Complications, Surgery **27:** 62, 1950.
10. Royce, S., Tepper, C., Watson, W., and Day, R.: Indwelling Polyethylene Nasogastric Tube for Feeding Premature Infants, Pediatrics **8:** 79, 1951.

OVARIAN AGENESIS (CONGENITALLY APLASTIC OVARIES) IN A 3-YEAR-OLD FEMALE

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ALTHOUGH ovarian agenesis (congenital aplasia of the ovaries) is being recognized with increasing frequency in adult females when sexual infantilism calls attention to the related gonadal deficiency, this diagnosis has seldom been made in children before the age of puberty. The purpose of this paper is to present a case of ovarian agenesis with clinical features of short stature, webbing of the neck, and "increased carrying angle of the arms" (cubitus valgus) in whom the tentative diagnosis was first made at the age of 2 years 11 months, and confirmed at the age of 4 years 1 month, when exploratory laparotomy and biopsy of the ovaries disclosed aplasia of these organs associated with a rudimentary uterus.

CASE REPORT

T. L. was first seen by one of us (C. H. C.) at the age of 2 years 11 months, because of shortness of stature. This child had been born at term after a normal pregnancy, labor, and delivery, and had weighed 6 pounds (2.73 kg.). The only abnormality noted in the neonatal period was "an excess amount of skin in the back of the neck." Her nutrition had always been adequate and supplemental vitamins had been given since early infancy. Her first deciduous tooth had erupted at the age of 7 months. Motor and mental development had seemed within normal limits. She had measles when she was 13 months old, whooping cough at 18 months (neither complicated nor severe), and sinusitis accompanied by a febrile convulsion at the age of 2 years 10 months. The family history was negative and no similar condition could be traced to any other member of the family. There were no siblings.

At the age of 2 years 11 months she had weighed 24 pounds 4 ounces (11.0 kg.), with a length of 31⅞ inches (81 cm.), head circumference 19 inches (48.2 cm.), wrists 3½ inches (8.8 cm.) in circumference, span 30 inches (76.7 cm.), crown to pubis 19 inches (48.2 cm.), pubis to internal malleolus 14 inches (35.6 cm.). Webbing of the neck was present and cubitus valgus (increased carrying angle of the arms) was noted. Blood chemistry studies showed fasting cholesterol 203 mg. per cent, blood urea nitrogen 14.7 mg. per cent, serum calcium 9.2 mg. per cent, phosphorus 4.2 mg. per cent, alkaline phosphatase 12.9 units per 100 c.c., and nonprotein nitrogen (during a period of dehydration in preparation for pyelography) 42 mg. per cent. The complete blood count and urinalysis were within normal limits.

Roentgenograms of the skull showed a normal cranial vault, normal appearing sella turcica, and no abnormal calcifications. Films of the chest showed a normal size and shape of the heart and clear lung fields. The bony thorax appeared normal. Roentgenograms of the long bones revealed epiphyseal development consistent with her age and no evidence of achondroplasia, or chondrodystrophy, or osteoporosis. Intravenous pyelography was performed. The excretion of dye was good and the kidney, pelvis, and the ureters appeared essentially normal. A tentative diagnosis was made of ovarian agenesis (Turner's syndrome).

She entered the University of California Hospital for further study in 1951 at the age of 4 years 1 month.

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Physical Examination.—She was a cooperative, well-developed and well-nourished child, of obviously short stature, who appeared of normal intelligence. Her height was 34½ inches (88 cm.), weight 28 pounds 13 ounces (13.1 kg.), chest circumference 52.5 cm., head circumference 48.5 cm., symphysis to foot length 34.25 cm., width of the chest between the two anterior axillary lines was 21 cm., crown to pubis 51 cm., pubis to internal malleolus 33 cm., wrist circumference 10.5 cm., distance between pubic spines 14 cm., distance between pubic crests 15¼ cm. Her skin was dry, without eruptions, and with no areas of abnormal pigmentation. Webbing of the neck was noted. Increased carrying angle at the elbows was present, and she had short, stubby hands (Fig. 1). A grade 1 systolic murmur could be heard over the apex of the heart. Peripheral pulsations were good. Blood pressure was 100/70.

She was seen by the gynecologic consultant, Dr. Ralph C. Benson, who stated that a very satisfactory single digital manipulation revealed "a minute nubbin" in the region of the uterine cervix, but nothing was felt in either adnexal region. The uterus could not be outlined.

Psychometric examination was performed and although it was not completely satisfactory because of poor cooperation, the intelligence quotient was believed to be at least 90. The ophthalmologic consultant found no abnormality of the eyes. The electrocardiogram revealed a record within normal limits.

Roentgenograms of thoracic and lumbar spine showed that the vertebral bodies were in good alignment, and epiphyses appeared normal. No evidence of osteoporosis was present.

Routine urinalysis was within normal limits, as was a complete blood count. Reaction to the Kolmer and Kahn tests was negative. On two occasions assay for pituitary gonadotropins was negative at 5 mouse units per twenty-four-hour urine specimen. Subsequently it was found to be negative at 1.25 mouse units per twenty-four-hour urine specimen. The 17-ketosteroids excretion was 0.8 mg. in a twenty-four-hour urine sample. The serum hormonal iodine was 0.5 mg. per 100 c.c. The reactions to the tuberculin and Schick tests were negative.

Fig. 1.—Photograph showing stocky build, broad shieldlike chest, webbed neck, and accentuated carrying angle of elbows.

On the basis of these findings our previous impression that we were dealing with a case of ovarian agenesis was strengthened, but since there was no elevation of urinary gonadotropins (as had been found in other children that we have seen with this condition) a definitive diagnosis could not be made. On March 13, 1952, the child re-en-

tered the hospital. Exploratory laparotomy and biopsy of the ovarian sites were performed by Dr. Ralph C. Benson. The uterus was found to consist of a small tubelike structure in the midline which was smaller than normal for a child of this age. The Fallopian tubes on either side were normal, but in the ovarian site only a whitish streak of fibrouslike tissue was noted. Biopsy of tissue from both the right and left ovarian sites revealed it to be composed primarily of fibrous connective tissue (Fig. 2). It contained numerous small capillaries but no evidence of germinal epithelium either covering the ovary or in primordial follicles was noted. There were a few collections of cells with small dark, round nuclei and very scant cytoplasm which might represent early granulosa cells. The pathologic diagnosis was agenesis of the ovaries.

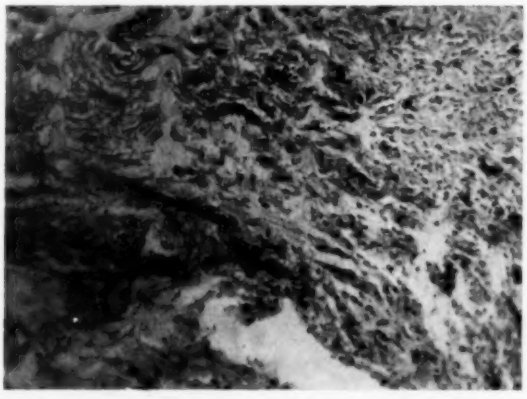

Fig. 2.—Photomicrograph of section of tissue from site of ovary.

The child withstood the operation very well and the postoperative course was uneventful.

DISCUSSION

In 1947 Goldberg and associates[1] reported the first case of ovarian agenesis in a prepubertal female. Their patient was a 12½-year-old girl with stunted growth, complete infantile appearance, and high urinary gonadotropin titer, who was found to have an "undeveloped uterus" and absence of normal ovaries, these structures being replaced by narrow streaks of glistening, grayish-white tissue which showed no evidence of follicular activity. Subsequently, van Crevald and De Vaal[2] observed "a girl 5 years old showing a complex of symptoms present in cases of ovarian agenesis. There was no enlarged excretion of gonadotropins such as is typical for the disease after puberty has been reached." Complete clinical or microscopic findings were not presented. Goldman and co-workers[3] have described an 8-year-old girl with shortness of stature, coaretation of the aorta, and abnormalities of the toes. No endocrine studies were reported and although the patient died at the time of operation for correction of the cardiac defect, no data were given regarding the ovaries.

Kaijser[4] described a 10-year-old girl with definite cubitus valgus, webbed neck, hypertension, normal bone age, and moderate osteoporosis. Only one assay of gonadotropins was reported and that was less than 40 mouse units per liter. On examination the uterus was found to be hypoplastic with a cordlike rudimentary ovary which histologically showed a cortical zone without any primary follicles. Marie and

associates[5] studied a girl between the ages of 13 and 14 years. She had shortness of stature, suggestion of hypertelorism, webbing of the neck, a short systolic murmur, "voluminous thorax," slender hips, and excellent muscular development. The clitoris was well developed but the genital organs were infantile. She had an occasional pigmented nevus on the extremities. Some osteoporosis was noted on roentgenograms. Gonadotropins were positive at 25 and negative at 50 mouse units. A rudimentary uterus was found at exploratory laparotomy and the ovaries were elongated whitish structures. Wilkins[6] described a 3-year-old patient of Drs. Goettsch and Lyttle who had dwarfing, asymmetry of face, webbed neck, and coaretation of the aorta, and in whom the FSH was less than 3 mouse units per day. In this child the diagnosis of ovarian agenesis was confirmed by laparotomy. He also reported a 12-year-10-month-old girl with shortness of stature and good muscular development who had a normal bone age but whose excretion of urinary gonadotropins was 192 mouse units per day. His third patient under the age of 14 years was a girl 13 years 5 months old with webbing of the neck and coaretation of the aorta who was the height of a 7-year-old child but had a bone age of 11 years 6 months and urinary gonadotropin assay of 192 mouse units per day.

Silver[7] has reported a complete study of a proved case with the characteristic signs of the syndrome, where elevated levels of urinary gonadotropins were found at the age of 2 years 8 months. The diagnosis was confirmed when exploratory laparotomy and biopsy of an ovary disclosed aplasia of these organs associated with a rudimentary uterus. Silver and Kempe[8] have described two girls with this condition, aged 8 years 10 months and 12 years 5 months, who had shortness of stature, good nutrition, and muscular development, broad shieldlike chests with widely spaced nipples, abnormally small uteri, and markedly increased excretion of urinary gonadotropins.

From a review of the pediatric literature, the most frequently described anatomic, biologic, and clinical prepubertal manifestations of the syndrome of ovarian agenesis have been:

(1) Shortness of stature of moderate degree.

(2) Good muscular development, the patients being strong, well nourished, and with a broad, shieldlike chest.

(3) Congenital anomalies, such as webbing of the neck, cubitus valgus, syndactylism, coaretation of the aorta, and ocular changes.

(4) Rudimentary ovarian development.

(5) Increased urinary gonadotropins.

(6) Moderate retardation of skeletal maturation with delay in epiphyseal closure.

Shortness of stature was noted in every one of the twelve cases in children under the age of 14 years (Table I) and was already a noteworthy finding in the three children less than 3 years of age. All of the girls were stockily built with good musculature and had the appearance of normal children somewhat younger than their chronological ages. In the cases that we have seen, wide spacing of the nipples producing a "shield-shaped chest"[9] was present, and in two instances it was one of the initial clues leading to studies which aided in making the diagnosis.

Various congenital abnormalities have been described in this syndrome, including cubitus valgus (increased carrying angle of the arm), pterygium colli (congenital webbed neck), pes cavus at rest, congenital deafness, coaretation of the aorta, and various ocular abnormalities. Of these, congenital webbed neck, coaretation of the aorta, and cubitus valgus are present most often in this syndrome. Webbed

TABLE I. CASES OF OVARIAN AGENESIS IN GIRLS UNDER 14 YEARS OF AGE AS REPORTED IN THE PEDIATRIC LITERATURE

CASE NO.	AGE DIAGNOSED	SHORTNESS OF STATURE	WEBBED NECK	CUBITUS VALGUS	CIRCULATORY DISEASE	MUSCULAR DEVELOPMENT	URINARY GONADOTROPIN TITER	BONE AGE	OSTEOPOROSIS	LAPAROTOMY		AUTHORS
										OVARIES	UTERUS	
1#	2 yr. 8 mo.	+	+	Slight	0	Good	Increased	Slightly retarded	0	Agenesis	Hypoplastic	Silver
2#	2 yr. 11 mo.	+	+	+	0	Good	Less than 2.5 m.u.	Normal	0	Agenesis	Hypoplastic	Cutler & Silver (present case)
3#	3 yr.	+	+		Coarctation of aorta	Good	Less than 3 m.u.			Agenesis		Wilkins
4†	5 yr.	+	+				"Very small"					Van Creveld & DeVaal
5†	8 yr.	+	0		Coarctation of aorta		Not determined		0	?	?	Goldman, Schroeder, and Futcher
6*	8 yr. 10 mo.	+	0	+	0	Good	Increased	Normal	0			Silver and Kempe
7#	10 yr.	+	+	+	Hypertension	Good	Less than 40 m.u.	Normal	+	Agenesis	Hypoplastic	Kaijser
8*	12 yr. 5 mo.	+	0	0	0	Good	Increased	Slightly retarded	+			Silver and Kempe
9#	12½ yr.	+	0	0	0	Good	Increased	Slightly retarded	0	Agenesis	Hypoplastic	Goldberg, Maxwell, and Smith
10*	?12 yr. 5 mo.	+	0			Good	192 m.u.	Normal				Wilkins
11*	?13 yr. 5 mo.	+	+		Coarctation of aorta	Good	192 m.u.	Retarded				Wilkins
12#	13 yr.	+	+		Short systolic murmur	Good	Increased	Retarded	+	Agenesis	Hypoplastic	Marie, See, Barcat, and Pette

#Proved cases.
*Probable.
†Presumptive.
(Adapted from Wilkins.)

neck was reported to be present in seven out of twelve patients in the pediatric literature; coaretation of the aorta in four; while cubitus valgus was present in three of the six patients in whom the presence or absence of this abnormality was mentioned. Our patient had congenital webbed neck, and a moderate degree of cubitus valgus, but no evidence of coaretation of the aorta or other circulatory disease was found.

No osteoporosis or delay in the bone age in relation to the chronologic age was noted in our patient. Although osteoporosis has been a relatively common finding in the older females, and was present in three of the six children between the ages of 10 and 14 years, it has not been described in any of the younger children. Retardation of the bone age has been reported in approximately one-half of the children but in no case has it been very marked, and it would appear that a pronounced delay becomes more evident after the normal age of puberty.

An increase in urinary gonadotropins is one of the most important single findings in making the diagnosis of ovarian agenesis. Although it was not elevated in our patient, increased excretion has been found in seven of the twelve cases in the pediatric literature, including one child at the age of 2 years 10 months. In the younger children the titers may be elevated *for the age* (our italics), but may be within the normal range for adult women in the reproductive age. At the age when puberty would normally be expected to occur the titers will reach levels higher than those of normal adults.

From this review of the literature of ovarian agenesis in children, it is apparent that no single diagnostic physical variation or laboratory finding is present in every instance. The girls are short and stockily built, but such changes may be seen in other conditions as well. Webbing of the neck, cubitus valgus, coaretation of the aorta and other congenital abnormalities were noted in many of the patients, but they are not indispensable parts of the syndrome. When markedly elevated titers of urinary gonadotropins are found in a stocky, short female, the diagnosis is almost certain, since excessive amounts of urinary gonadotropins are rarely found in any other disease of childhood, but not every child with proved ovarian agenesis has had an increased excretion of gonadotropins, as the present case demonstrated. In the adult cases, primary amenorrhea and signs of sexual infantilism are prominent, but it is possible to make the diagnosis at a time of life before such findings are evident.

Ovarian agenesis must be differentiated from other diseases which retard growth or modify the development of the sexual organs. In most cases, a differential diagnosis may readily be made by a suggestive clinical picture and the performance of the proper diagnostic tests, but in some instances only surgical exploration will give a definitive answer.

SUMMARY AND CONCLUSIONS

A proved case of the syndrome of ovarian agenesis, short stature, and multiple congenital abnormalities in a 2-year-11-month-old female is presented.

Congenital anomalies included webbed neck and a moderate degree of cubitus valgus.

At exploratory laparotomy the patient was found to have typical whitish fibrous "streaks" in the ovarian sites and a hypoplastic uterus.

The pediatric literature on ovarian agenesis is reviewed.

REFERENCES

1. Goldberg, M. B., Maxwell, A. F., and Smith, P. M.: Three Unusual Endocrinopathies With Associated Ovarian Pathology: I. Ovarian Agenesis: II. Precocious Puberty: III. Virilism, J. Clin. Endocrinol. 7: 11, 1947.
2. Van Crevald, S., and De Vaal, O. M.: A Case of Ovarian Agenesia. Acta paediat. 37: 474, 1949.

3. Goldman, M. L., Schroeder, H. A., and Futcher, P. H.: Coaretation of the Aorta Associated With Abnormal Digits, Ovarian Insufficiency and Shortness of Stature, J. Clin. Endocrinol. 9: 622, 1949.

4. Kaijser, K.: Sexual Infantilism With Rudimentary Ovaries, Acta endocrinol. 3: 351, 1949.

5. Marie, J., See, G., Barcat, J. R., and Pette, F.: Presentation d'une enfant atteinte de Maladie de Turner-Albright, Arch. franç. pediat. 7: 153, 1950.

6. Wilkins, L.: The Diagnosis and Treatment of Endocrine Disorders in Childhood and Adolescence, ed. 1, Springfield, Ill., 1950, Charles C Thomas.

7. Silver, H. K.: Syndrome of Ovarian Agenesis (Congenitally Aplastic Ovaries), Short Stature, Multiple Congenital Abnormalities and High Urinary Gonadotropins in a Two Year, Eight Month Old Female, Pediatrics 8: 368, 1951.

8. Silver, H. K., and Kempe, C. H.: Ovarian Agenesis (Congenitally Aplastic Ovaries) in Children, Am. J. Dis. Child. In press.

9. Lisser, H., Curtis, L. E., Escamilla, R. F., and Goldberg, M. B.: Syndrome of Congenitally Aplastic Ovaries With Sexual Infantilism, High Urinary Gonadotropins, Short Stature and Other Congenital Abnormalities, Tabular Presentation of Twenty-five Previously Unpublished Cases, J. Clin. Endocrinol. 7: 655, 1947.

HYPERTROPHIC PYLORIC STENOSIS ASSOCIATED WITH ADRENAL INSUFFICIENCY

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THE purpose of this report is to record a case of hypertrophic pyloric stenosis associated with congenital adrenal insufficiency. Both of these pathologic states give a similar clinical picture early in their course, so much so that if a patient has equivocal evidence of hypertrophic pyloric stenosis he should not be surgically explored until adrenal cortical insufficiency has been ruled out.

F. G., a 14-day-old white male infant, was first seen in the emergency ward of the Indianapolis General Hospital. Informant was the baby's 18-year-old mother who stated the child was brought in for medical care because of malnutrition, diarrhea, and vomiting.

The patient was delivered normally after an uneventful full-term pregnancy at a near-by Army Hospital with a birth weight of 6 pounds 13 ounces. Breast feeding was not attempted due to the mother's inverted nipples. The patient never seemed to eat properly, taking only 1 ounce of formula (13 ounces evaporated milk, 19 ounces water, 2 T. Karo) at a time. He was somewhat lethargic since birth and would have a small, green, semiliquid bowel movement two to three times a day. He weighed 6 pounds 9½ ounces when discharged on the fifth day. Vomiting began on the fifth day of life. It was small in amount, brownish at first and then green in color. There was no time relationship to feedings. On the eleventh day the character of the vomiting changed. It became projectile and usually occurred within one-half hour after feedings. The patient became anorexic, very lethargic, and lost 1 pound 7 ounces during the three days preceding admission.

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Family history revealed the mother had been "anemic for years" and had menorrhagia. The father, aged 22, is in the U. S. Army and is in good health. No history of heredofamilial diseases was elicited.

Physical examination disclosed a severely ill white male infant who weighed 5 pounds 1 ounce and who had a rectal temperature of 99.2° F. He was quite lethargic, had depressed respirations, and was severely dehydrated. There was visible gastric distention with peristaltic waves after a feeding of glucose water. One examiner felt a pyloric tumor. The skin revealed a severe "sweat" rash generalized but most severe of the scalp. The examination was otherwise normal. The patient was taken to the x-ray department where multiple films of the abdomen revealed "only a gas-filled stomach. There is no air seen in the large or small bowel." Lipiodal study showed pyloric obstruction. A tentative diagnosis of hypertrophic pyloric stenosis was made and the infant was admitted to the hospital. Admission complete blood count and urine were within normal limits considering the severe dehydration. Initial therapy consisted of parenteral fluids, an incubator, and oxygen. Approximately twenty-four hours after admission he was taken to surgery where under ether anesthesia an exploratory laparotomy was done by Drs. Joseph Manning and Ralph Thomas. A large pyloric tumor was found and a classical Ramstedt procedure was done. Postoperatively he was given a transfusion and parenteral fluids. When oral feedings were attempted on the second postoperative day he again vomited all feedings and continued to have loose stools. In spite of good wound healing, no disten-

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tion, good bowel sounds, a trial of phenobarbital and belladonna, he continued to be unable to tolerate oral feedings for four weeks, being maintained on parenteral fluids. On the thirtieth hospital day he was dehydrated, acidotic, and weighed 5 pounds 4 ounces. Adrenal cortex extract 1 c.c. q. 8 h. in addition to parenteral fluids was started and within two days he began tolerating oral feedings and gaining weight. In a week he was out of his incubator and no longer needed oxygen, and weighed 6 pounds 10 ounces. Blood studies at this time showed $K^+ = 5.1$ meq., $Na^+ = 14.0$, $Cl^- = 109$ meq. As a therapeutic trial the adrenal cortex extract was stopped and he went downhill to 5 pounds 15 ounces in three days. Adrenal cortex extract was restarted and he again got along well. One week later the adrenal cortex extract was again stopped as a therapeutic trial and again he went downhill. He was restarted on desoxycorticosterone acetate (Cortate) 2½ mg. daily, with 3 Gm. of salt added to his formula. He was released on the sixtieth hospital day weighing 7 pounds 9 ounces.

He was followed in the outpatient department, receiving daily desoxycorticosterone acetate for about one month. Two months after discharge he weighed 12 pounds 12 ounces and was on a normal full diet.

DISCUSSION

This infant had done poorly since birth, with vomiting and diarrhea, then the development of signs of pyloric obstruction. His adrenal insufficiency was masked by administration of parenteral saline. The diagnosis became evident when his pyloric obstruction was relieved and he continued to have acidosis and dehydration which responded only to adrenal hormone therapy. Adrenal insufficiency must be suspected in a newborn infant with diarrhea and vomiting, water loss, or failure to gain properly. For confirmation the best test is a therapeutic test with adrenal hormones. Blood Na^+, K^+, Cl^-, CO_2 combining power, and eosinophil counts and urinary chlorides are suggestive but inconclusive.

This case arouses interesting speculation beyond the scope of this paper to prove or disprove as to the possible causal interrelationship of adrenal cortical insufficiency and hypertrophic pyloric stenosis. The hypertrophy of the pyloric muscle is categorically similar to fibrotic hypertrophy of the collagen-rheumatoid diseases which respond to cortisone and corticotropin therapy. The natural history of the pyloric muscle tumor is that it recedes whether treated with or without surgery during the time the adrenal cortex is changing to an adult type anatomically and physiologically.

SUMMARY

A case of pyloric stenosis associated with adrenal insufficiency is reported. The infant received adrenal hormones from age 6 weeks to 4 months. At the time of this writing he is 5 months old and progressing normally. A possible causal relationship between adrenal cortical insufficiency and hypertrophic pyloric stenosis is postulated.

CONGENITAL TOTAL HYPERTROPHY OF THE RIGHT UPPER LIMB

"Right-Armed Acromegaly"

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THE literature dealing with hypertrophy of various parts of the body has been carefully reviewed by Ward and Lerner[1] who at the same time compiled a comprehensive classification of the subject. The great majority of cases reported deal with congenital hemihypertrophy or acquired hypertrophies from various causes. True hypertrophy affecting all the structures of a limb is extremely uncommon and I have been able to find only one case[2] comparable to the one reported here.

CASE REPORT

A. B., a male child, aged 9 years, attended the outpatient clinic of Prof. F. A. R. Stammers in February, 1952, because of asymmetrical growth of his arms.

His earlier history was not quite clear, but it was established that for at least four years his parents were aware that the right arm was noticeably larger than the left, and that the disproportion was increasing. His teacher called attention to the boy's increasing clumsiness in writing with the result that the patient had begun to practice writing with his left hand. Apart from this his progress at school was good and equal to boys of similar age. The boy himself was aware that the right arm and hand were bigger and stronger than the left and admitted that its hitting power had impressed his schoolmates. He was the elder of a family of two boys and there was no record of any growth deformity in the family history.

Physical Examination.—The patient was an intelligent and normal looking boy of 53 inches (134.6 cm.) in height and weighing 63 pounds (28.7 kilograms). Except for the right upper limb he appeared to be of average normal development for his age, and routine systematic examination, including x-ray of chest and skull, failed to reveal any evidence of further disorder.

The striking feature of the right upper limb was its muscular development. It recalled the description of von Brucke[2] that the appearance suggested a wrestler or weight putter (Fig. 1). The skin of the right upper limb was normal in texture and color and was supported by no more subcutaneous fat than on the left arm.

The hypertrophy affected all the muscles of the shoulder girdle, both front and back being particularly obvious in the case of the pectoral, rhomboid, and spinati muscles. The power was not measured accurately but appeared to be approximately twice that of the left arm for all movements of the shoulder, elbow, and wrist. Muscle coordination in respect of movement about these joints was normal (Fig. 2).

The hand was the only part where deformity was present. The great mass of thenar muscles seemed to keep the thumb abducted and hypertrophy of the lumbricals interossei muscles may have been the cause of

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the increased distances between the metacarpal heads (Fig. 3). The grip was powerful and readily sustained, but fine movements were clumsy, and the index finger was held habitually in a position of gross ulnar deviation which, combined with thumb abduction, gave the hand a simian appearance.

Special Examinations.—To exclude the possibility of an arteriovenous shunt of any kind within the arm, various tests were carried out. (1) Compression of the axillary artery had no effect on the pulse rate. (2) The O_2 content of the superficial venous blood was similar on both sides. (3) The blood pressure in each arm was 90/65, and (4) the skin temperature gradient was exactly equal on each side, although there was a 20 per cent increase in oscillometric fluctuation on the right.

Fig. 1.—Photograph showing the remarkable muscular development and increase in size of the right arm.

Fig. 2.—Photograph showing the hypertrophy of the deltoid, the pectoralis muscles, and latissimus dorsi muscle. The size of the hypothenar muscles in comparison with those in the left hand can be noted.

There was a postural scoliosis to the left, apparently due to the weight of the shoulder girdle, and the patient showed a tendency to stand with his head inclined to the right side.

Fig. 3.—Illustrating the position of ulnar deviation of the right index finger and the increased span of the right hand.

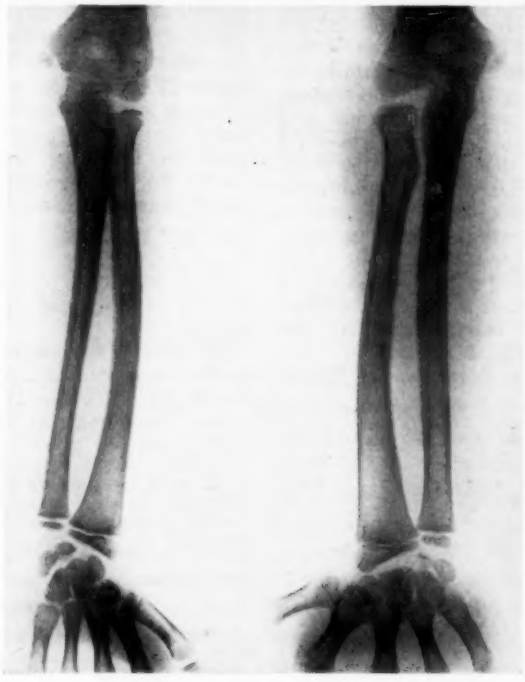

Fig. 4.—X-rays of both forearms and both metacarpals (see text.)

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Measurements. — Measurements of the arm were as follows:

	Right (cm.)	*Left (cm.)*
Length of arm (acromion to external humeral condyle)	27.9	26
Length of forearm	20.9	19.7
Length of fingers		
Index	7.6	7.6
Middle	8.6	8.6
Ring	8.2	7.6
Little	6.3	6.3
Maximum girth upper arm	24.8	18.4
Maximum girth forearm	22.9	17.8
Girth of palm at thenar web	22.6	16.5
Girth around shoulder at axilla	40.3	28.6
Spine 7th C.V. to A-C joint	17.4	14.6
Span of hand (thumb to 5th finger)	20.3	16.5
Span of hand (index to 5th finger)	12.7	12.7
Hemithorax (at nipple level—in expiration)	39.3	34.3

X-ray Examination.—X-ray examination of both upper extremities confirmed that the increase in size of the right upper limb affected the length and width of the scapula, clavicle, humerus, radius, and ulna. The texture of these bones appeared normal and where comparable measurements could be made from the x-ray plates these are given. The digital phalanges showed no appreciable differences in length or strength but the metacarpals of the affected hand, while much thicker and stronger than those of the other side, were, in some cases, shorter and separated considerably at the palmar ends (Fig. 4).

Measurements From X-ray Plates:

	Right (cm.)	*Left (cm.)*
Radius	19.5	18.5
Ulna	20.0	19.1
Scapula (from interior angle to superior angle)	12.7	11.0
Metacarpal		
1st	3.9	3.7
2nd	4.2	4.8
3rd	4.3	4.6
4th	4.4	4.3
5th	4.1	4.0

Distance between metacarpal heads, measured at the center of the heads of the metacarpals:

	Right (cm.)	*Left (cm.)*
Between metacarpal		
2nd & 3rd	1.0	0.7
3rd & 4th	1.2	0.7
4th & 5th	1.8	0.7

COMMENT

Sir A. Keith[3, 4] has put forward the theory that true segmental hypertrophy, or by his definition "local acromegaly," is a disorder of the mechanism which produces local hypertrophy from normal causes (as in a blacksmith's arm). In this case he postulates a local increase in susceptibility to the growth hormone. He has also drawn attention to the prominence of the nuchal and occipital parts of the trapezius on *both* sides.

Von Brucke[2] who recorded a case similar to mine in great detail noted that at birth the hypertrophied limb was slightly shorter than its fellow but at the age of 3 years this discrepancy had corrected itself. He also noted the fullness of the palm and abnormality of habitual position of the thumb and index finger which he attributed to muscle pull. He quotes the views of others that there is a tendency for the hyperplastic muscles in such cases as these to change to fatty tissue with progressive deterioration in muscular power. There is as yet no evidence that this tendency has begun in the case recorded here.

SUMMARY

1. A case of true segmental hypertrophy of the right upper limb is recorded.

2. Except for some diminution in ability to perform fine digital movements, no tendency to loss of muscle power has become apparent at the age of 9 years.

It gives me pleasure to acknowledge the help and advice I have received from Sir Arthur Keith and Mr. A. J. Rains in connection with this case and to express my thanks to Mr. T. F. Dee for the photographic reproductions.

REFERENCES

1. Ward, J., and Lerner, H. H.: J. PEDIAT. **31**: 403, 1947.
2. Von Brucke, H.: Virchow. Arch. f. path. Anat. **296**: 681, 1936.
3. Keith, Sir A.: Personal communication to Mr. A. J. Rains, July, 1952.
4. Keith, Sir A.: Bull. John Hopkins Hosp. **33**: 155, 195, 1922.

Medical Progress

ACRODYNIA AND MERCURY

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A PAPER by us entitled "Adverse Mercurial Reactions in the Form of Acrodynia and Related Conditions" was published in March, 1951.[83] Although written in 1949, its publication was delayed. Since that time additional data have been accumulated and at least fifty relevant publications have appeared in the literature. The contributions have come from many countries, some of them in journals not easily accessible to the American reader. Interest aroused by the etiologic relationship between acrodynia and exposure to relatively small amounts of mercury has also led to the discovery of other manifestations of mercurial hypersensitivity. The circumstances call for and justify another review of the subject.

Between October, 1949, and June, 1952, urine specimens from twenty-eight acrodynic children have been examined in the Kettering Laboratory. Only five patients were observed in the Children's Hospital of Cincinnati; we are indebted to pediatricians in other cities for urine samples and case histories in the remaining twenty-three cases.

In twenty patients the history revealed exposure to mercury. The sources were calomel-containing teething powders in eight cases; calomel tablets or powders, five cases; calomel-containing worm medicines, four cases; ammoniated mercury ointment, one case; bichloride of mercury used as a diaper rinse, one case. One child had been given calomel and later smeared ammoniated mercury over his face and into his mouth.* In two cases various drugs and laxatives had been prescribed but their composition could not be ascertained and in six patients no history of exposure to mercury was obtainable.

Mercury was found in the urine of eight patients in whom there was no definite history of exposure. Significant amounts were also found in the urine of seventeen of the twenty children whose histories clearly indicated exposure. In three patients from whom only single specimens were submitted the urine was free of significant amounts of mercury, but it was known that these patients had taken calomel-containing preparations. *Thus it was shown that all the acrodynic children of this series had been exposed to mercury.* These findings, as well as those reported by authors from many other parts of the world, support the hypothesis that acrodynia is an effect of exposure to mercury. However, in countries where 40 to 50 per cent of the children are habitually given calomel[61, 66] observers see that hundreds of children ingest mercurial preparations without ill effects. It is understandable, therefore, that authors in France,[30, 61] Belgium,[32] and England[57] have confirmed our findings but are hesitant to accept our conclusions. By summarizing all the arguments available at the present time we shall

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*Case 3. This case has been reported in detail by Silverman and Cassady.[77]

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TABLE I

CASE NO.	AGE AND SEX	OUTLINE OF CLINICAL COURSE OF ACRODYNIA	URINARY MERCURY μg PER LITER	SOURCE OF MERCURY	DIMERCAPROL TREATMENT	OUTCOME
1.	B. L. 5 yr. M	Morbilliform rash, anorexia, pink palms and soles, pruritus, irritability, increased perspiration, conjunctivitis, rubbed eyes. Pulse 140; Blood Pr. 120/98	Before BAL: 100 1 day after BAL: 220 3 days after: 220 4 days after: 100 7 days after: 280 9-11 days after: 0 0 0	Calomel and santonin for worms	+	Improved
2.	A. 9 mo. F	Irritability, fretfulness, sleeplessness, excessive perspiration, rash, fever, red hands and feet, rubbed feet together. Pulse 160; Blood Pr. 130/90	510	Bichloride of mercury used as diaper rinse	−	Recovered slowly
3.	S. B. 2½ yr. M	Irritability, sleeplessness, anorexia, rash, hands and feet pink, swollen, desquamating, pruritus, salivation, conjunctivitis, poor muscle tone, weakness. Pulse 180; Blood Pr. 140/110	20 50 30 After 8 days of BAL treatment: 10 90 10 days after: 80 230	Calomel. Ammoniated mercury ointment	+	Much improved
4.	McK. 1½ yr. M	Irritability, sleeplessness, loss of weight, "bites and scratches," swollen and red gums, pink palms, weak muscles	120 90 3 mo. after BAL < 10	Various laxatives	+	Unknown
5.	B. H. 4 yr. F	Abdominal pain, anorexia, loss of weight, rash, pink palms and soles, which she rubbed because of burning and itching, muscular weakness. Falls forward. Pulse 132	480	Unknown	−	Unknown
6.	R. A. T. 14 mo. F	Irritability for 2 mo., photophobia, rash on hands, feet and trunk, "wants her feet scratched," palms and soles red and exfoliating. Pulse 165; Blood Pr. 254/180	70 60	Unknown	+	Unknown
7.	C. H. 8 mo. M	Onset at age of 4 mo., upper respiratory infection, irritability, restlessness, photophobia. Rash involving back of neck, abdomen, groin. Hands cold but not red. Blood Pr. 150/60	80 After BAL: 60	Calomel tablets	+	Photophobia and irritability improved. Blood Pr. 95/55

TABLE I (CONT'D)

TABLE I (CONT'D)

CASE NO.	AGE AND SEX	OUTLINE OF CLINICAL COURSE OF ACRODYNIA	URINARY MERCURY μg PER LITER	SOURCE OF MERCURY	DIMERCAPROL TREATMENT	OUTCOME
8.	W. C. 7 mo. M	Onset at age of 4 mo. with papular rash over entire body lasting 3 weeks, followed by irritability, photophobia and redness of face and hands and "failure to do well"; rash 3 days prior to admission after further use of teething powders. Blood Pr. 150/100	30 After BAL: 90	18 teething powders prior to onset of disease 14 more powders given during 2 wk. prior to admission	+	Improved. Was asymptomatic 30 days after completion of BAL treatment
9.	P. M. 14 mo. F	Irritability, red palms and soles, cold hands and feet. Blood Pr. 170/110	260	Unknown	None	Unknown
10.	L. B. 9 mo. M	Onset at age of 6 mo., low-grade fever, generalized rash, marked irritability and fretfulness, rubbing of hands and feet, continual scratching; progressive weakness, bizarre positions. Blood Pr. 118/72	40	At age of 5 mo. 24 mercurial teething powders	+	Comfortable after course of BAL. Reported "feeling fine" 1 mo. after discharge.
11.	J. S. 2½ yr. M	Irritability, insomnia, excessive perspiration, loss of appetite and weight, rash, itching and peeling, redness of tip of nose, bizarre positions. Blood Pr. 140/95, Pulse 140. Plasma sodium 150 meq. per liter	100 130	Unknown	+	Greatly improved immediately; now well
12.	J. P. 2 yr. F	One month after worm pills, morbilliform rash; one month after rash, diarrhea, irritability, anorexia, loss of weight, abdominal pain, erythema of soles and palms, reflexes hypoactive. Blood Pr. 110/70; Pulse 104	470 After BAL: 60	18 mercurial worm pills for ascariasis	+	Appetite, disposition improved during treatment. Well 5 wk. later
13.	H. 3 yr. F	Two weeks after worm treatment listlessness, irritability, anorexia, loss of weight, abdominal pain, change of personality; 3 wk. later perspiration, rash on back, arms and feet, desquamation; one week later generalized convulsions, muscular twitching, confused, rocking back and forth, reflexes hyperactive. Pulse 100-200; Blood Pr. 140/100	100	Santonin-calomel 2 wk. before onset of disease	+	General improvement but had behavior disorder on discharge
14.	R. P. 3 yr. F	Irritability, anorexia, restlessness, abdominal pain, painful palms and soles, loss of 12 pounds	50	Unknown but had laxatives, worm treatment, tonics, etc.	None	No change during hospitalization
15.	J. C. M	Restlessness, continuous crying, loss of weight, redness of hands and feet, perspiration, desquamation, photophobia, leg pains, generalized weakness.	25 55 25	Calomel	+	Steady, gradual improvement

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TABLE I (CONT'D)

CASE NO.	AGE AND SEX	OUTLINE OF CLINICAL COURSE OF ACRODYNIA	URINARY MERCURY μg PER LITER	SOURCE OF MERCURY	DIMER-CAPROL TREATMENT	OUTCOME
16.	S. McC. 1 yr. F	Onset of irritability, crying, sleeplessness 1 mo. after administration of first powders. Anorexia, photophobia, bizarre positions, hands and feet dusky red. Blood Pr. 110/80.	390 3 days after BAL: 2,000	Many calomel-containing powders given	+	Unknown
17.	C. H. 14 mo. F	"Aerodynia"	570	Calomel-containing teething powders	–	Unknown
18.	D. H. 8 mo. M	Restless, sleepless, marked photophobia, cold perspiration, morbilliform rash, bluish red color of hands and soles, arms and legs painful, anorexia	50	Teething powders 3 mo. before outbreak of disease and again during course of disease	+	Marked improvement of sleep, appetite when treatment was started
19.	T. H. 6 mo. M	Irritability, sleeplessness, marked photophobia, rash, palms and soles pink. Blood Pr. 135/90; Pulse 180	40 2 mo. after BAL: 40	Unknown	+	Very slow improvement for 3 mo. in spite of BAL treatment. Then recovered.
20.	F. B. 11 mo. M	"Aerodynia"	0 5 mo. after adm. of teething powders	Teething powders	None	Cured 4 wk. after therapy with liver extract, inj., synkavite, etc.
21.	C. S. 9 mo. F	Lack of appetite, no gain in weight for 4 mo. Physical retardation. Increased perspiration. Hands and feet cold and slightly flushed. Slight maculopapular rash. Blood Pr. 110/70; Pulse 120	20 During BAL treatment 180	Ammoniated mercury ointment	+	Improved
22.	B. G. S. 8 mo. F	Irritable, restless during sleep, salivation, anorexia, photophobia, increased perspiration, pink face, neck, palms, soles and toes; skin of toes peeling; occasional low-grade fever. Blood Pr. 106/74; Pulse 160	120	Teething powders 2 mo. before admission and determination of urinary mercury	–	One month later reasonably improved
23.	G. E. M. 3 yr. M	After treatment of ascariasis child developed pain in abdomen and knees, irritability, redness of nose, fingers, and toes, rash over entire body, desquamation, itching, liver palpable. Blood Pr. 142/84; Pulse 156	610	Teething powders 1 yr. before. Calomel-containing worm medicine 3 mo. before admission and determination of urinary Hg. Later 3 more worm treatments of unknown composition	+	Slight improvement
24.	B. W. 16 mo. F	Irritability, photophobia, excessive perspiration, rash, hands, feet, and face red, gums swollen and red, poor muscle tone. Pulse 140.	420	Unknown	–	Slow recovery

TABLE I (CONT'D)

CASE NO.	AGE AND SEX	OUTLINE OF CLINICAL COURSE OF ACRODYNIA	URINARY MERCURY μg PER LITER	SOURCE OF MERCURY	DIMER-CAPROL TREATMENT	OUTCOME
25.	J. H. 3½ yr. F	Irritability, anorexia, itching, rash and swelling of hands and feet, excessive perspiration, loss of weight. Blood Pr. 140/98; Pulse 130	8 (Before therapy)	Calomel as vermifuge	+	Improved very slowly
26.	C. 2 yr. F	For 3 mo. irritability, insomnia, weakness, red hands, feet, and nose, desquamation, ulceration beneath tongue. Blood Pr. 140/90; Pulse 180	0 (Before therapy)	Teething powder	+	Dramatic response to treatment
27.	J. B. 13 mo. M	Acrodynia	270	Calomel 3 wk. before onset of symptoms	–	Unknown
28.	3½ yr. F	Irritability, anorexia, loss of weight, moderate fever, perspiration, pinkness of palms and soles, rubbed fingers and toes, bizarre position. Blood Pr. 130/98 to 150/120; Pulse 152.	50	Calomel	–	Discharged after short observation unimproved

For supplying histories and urine specimens we are indebted to Dr. N. W. Ryan (Case 1), Dr. C. F. Wagner (Case 2), Dr. H. A. Cassady (Case 3), Dr. A. A. Weech (Case 4), Dr. H. F. Downing (Case 5), of Cincinnati; The Department of Pediatrics, Vanderbilt University, Nashville, Tenn. (Cases 6, 7, 8, 9, 10, 11, 21); Department of Pediatrics, University of Kansas, Kansas City, Kan. (Cases 12, 13, 14); Dr. T. G. Folsom, Huntington, W. Va. (Case 15); Dr. W. Hall, Charlotte, N. C. (Case 16); Dr. L. E. Metcalf, Asheville, N. C. (Case 17); Dr. B. M. Beach, Columbus, Ga. (Case 18); Dr. C. K. Pitt, Decatur, Ala. (Case 19); Dr. W. Weston, Jr., Columbia, S. C. (Case 20); Department of Pediatrics, Bowman Gray School of Medicine, Winston-Salem, N. C. (Cases 22, 23); The Bowman Clinic, Johnson City, Tenn. (Cases 24, 25, 26); Farren Memorial Hospital, Montague City, Mass. (Case 27); Department of Pediatrics, University of Michigan, Ann Arbor, Mich. (Case 28).

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attempt to prove our conception of acrodynia as an adverse reaction to mercury.

1. If properly searched for, exposure to mercury can be proved in all acrodynic children.
2. In many respects acrodynia resembles well-known reactions to mercury.
3. In some patients acute reactions to mercury develop into acrodynia.
4. The varying age distribution in different areas can be explained by local "mercurial habits."

EXPOSURE TO MERCURY

As in our present series, calomel has been the most frequent source of mercury in the cases of acrodynia recently published. As pointed out by Fanconi and associates[37] acrodynia often follows worm treatment with calomel-containing anthelmintics and in many recent reports these findings have been confirmed.[3, 4, 32, 61, 69, 73, 88] In other cases calomel was given for constipation,[62] diarrhea,[88] cough,[16, 25] or for unspecified reasons. In England,[41, 46, 53, 57] in the southern United States,[12] and in East Africa,[55] calomel was usually ingested in the form of teething powders. Holzel and James[53] re-examined 110 children in whom pink disease had been diagnosed in one hospital in Manchester, England, from 1930 to 1950. In ninety-seven cases a definite answer was given to the question whether or not teething powders had been used. Although in many instances the disease had occurred many years before re-examination, it was ascertained that 50 per cent of the children had been given mercurial teething powders. In the same area only 6.9 per cent of the healthy infant population were in the habit of taking mercurial teething powders. It is not stated whether the interrogators considered sources of exposure to mercury other than teething powders. Mercurial ointments have been recognized repeatedly as the source of mercury.[5, 27, 30, 32, 44, 77, 88, 90] In three instances[5, 77] the ointment was not only applied to the skin but also inadvertently ingested. Among these a case of Silverman and Cassady[77] is of special interest because a definite history of exposure was obtained only recently, although the child had had acrodynia more than ten years ago at a time when the mercurial origin of the disease was not yet recognized. For the same reason a report by Wiedemann in 1944[87] is of special value. This author described a case of "mercury poisoning" following treatment with ammoniated mercury ointment in a 3-year-old boy who developed agranulocytosis and acrodynic symptoms in the course of the disease. Two cases of acrodynia following the use of bichloride of mercury diaper rinse were reported by McCoy.[71] To these known sources of mercury some new ones have been added. Fischer and Hodes[39] described a case of acrodynia which followed treatment of warts with protiodide of mercury given in the form of pills. Kirk[58] observed an acrodynic girl, 21 months old, whose mother "denied any exposure to mercury in powders, ointments or liquids; but three days later she brought in some white wafers with which the patient had been playing for the last month. Her mother said they were chemical 'heat tablets,' and on analysis they proved to contain mercuric sulfocyanide." In two instances acrodynia followed mercurial inunctions given for suspected syphilis.[7, 26] These publications are significant since they refute the statement made sometimes

that acrodynia never followed mercurial antisyphilitic treatment. In addition to oral and cutaneous administration the possibility of rectal therapy must not be forgotten since some suppositories contain mercury.[61] How difficult it may be to ascertain the source of mercury is well illustrated by a case reported from Norway by Andersen.[2] In an acrodynic child, 20 months old, no history of exposure to mercurial drugs could be obtained. Although the urine contained 368 μg. of mercury per liter, analyses of ointments and medicines which had been given to this child were found to be free of the metal. This did not satisfy the author: "It was discovered that the family lived in the same house as another family which had its income from a small gilding industry operated in the same building. Corrosive mercury chloride is commonly used in the process of gilding and silver plating. The owner of the industry denied that corrosive mercury chloride had been used. It was found out, however, that he obtained a license for buying this substance and that he had actually bought it. The patient's father used to work in the place during spare hours and her six year old brother used to play there often. It happened that the boy brought with him to his home articles manufactured in the place. Circumstantial evidence of exposure to mercury thus seemed to exist in the case reported."

These cases illustrate the difficulties encountered in attempts to prove exposure to mercury by history alone. The statement that a child has not taken teething powders certainly does not exclude exposure to mercury. Not only are there many other sources of mercury accessible to children, but they may have escaped parents and physicians alike. In an acrodynic child exposure to mercury cannot be excluded by history alone; even the most careful negative history must be supplemented by a search for mercury in the urine.

In the majority of the cases recently reported, mercury was demonstrable in the urine when searched for by proper methods. Kirk[58] and Armaingaud[3] demonstrated urinary mercury in all their patients, and so did Denys[32] in the four patients whose urines were examined. Many reports of single cases were also positive.[16, 26, 27, 41, 59, 63, 73, 77, 81] Ivady and co-workers[56] made a valuable contribution by testing serially the urine of three acrodynic children and of forty-eight controls. Measurable amounts of mercury were found exclusively in the urine of the acrodynic patients. Laplane and associates[61] showed the presence of the metal in eight of nine patients with acrodynia. Zellweger and Wehrli[95] found mercury in ten of eighteen acrodynic patients who had mercurial medications; in four patients with the same diagnosis, in whom no history of such medications was obtained, and in eighteen control patients, no mercury was detected in the urine. Holzel and James[53] examined ninety-four children with active acrodynia. In sixty-one (or 65 per cent) increased amounts of mercury ranging from 200 to 2,500 μg per liter were found. These authors state that no abnormal excretion was detected in thirty-three (or 35 per cent) of the patients but it is not clear how many excreted significant amounts under 200 μg per liter. Debré and collaborators,[30] reporting seven acrodynic patients, found more than 100 μg of mercury per liter in six of them

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and less than 100 μg in all of their twelve controls. James[57] recovered significant amounts of mercury (over 50 μg per liter) from six typical and five atypical acrodynic patients. However, fifteen of their sixteen control patients also eliminated measurable quantities of mercury, though in lesser amounts. This surprising fact will be discussed later.

Determination of mercury in the urine is of particular value in acrodynia when a history of exposure cannot be obtained. Such was the case in eight patients of our series and in some reported elsewhere.[2, 32, 61] In certain instances a positive history was obtained after the results of urinalysis had proved exposure. On the other hand, it must be emphasized that occasionally exposure can be proved by history while the urinalysis is negative. This was the case in patients 20, 25, and 26 of our series and in several patients recently reported.[25, 54, 69, 88] Failure to find mercury in the urine while the metal is present in the body may be due to various circumstances. Insufficient amounts of urine used for analysis or employment of an insensitive method accounts for some of the negative results. Such errors need not be discussed here, since we have described the method used in our analyses[83] and since other authors who have used different but adequate methods have obtained results comparable to ours. But it must be re-emphasized that the urinary elimination of mercury is capricious and may vary from day to day or from hour to hour. This is shown in Table II which lists the mercury excretion of a 3-year-old child who developed acrodynia following treatment of impetigo with 5 per cent ammoniated mercury ointment four weeks before onset of the disease (Case 10 of our previous series[83]): Although the acrodynic symptoms disappeared rapidly, the child's urine specimens were examined over a period of a year. Usually, morning, noon, and evening samples were submitted.

TABLE II

DATE	URINARY MERCURY μg PER LITER
8/47 5% ammoniated mercury ointment applied (about 4 tubes of 3 oz. each)	
9/47 Onset of acrodynia	
10/24/47 Admitted to hospital	14
10/26/47	72
	40
	0
11/ 3/47 Clinically improved	
11/ 8/47 Much improved, discharged	
11/11/47 Clinically well	80
	60
	40
11/19/47	40
	80
	50
11/28/47	70
	100
	50
12/ 5/47	50
	60
	70
1/26/48	20
	70
	50
2/28/48	30
	30
	30
6/ 2/48	50
	80
	30
9/25/48	0
1/29/49	0
	0
	0

Table II shows that this patient, who excreted mercury rather regularly for at least nine months, had among his first urine specimens one that was mercury-free. Since it is fairly certain that this child was not re-exposed dur-

ing the period covered by the determinations, we can assume that his tissues contained substantial amounts of the metal when the negative sample was obtained on Oct. 26, 1947. In another case of our first series (Case 27),[83] the elimination of mercury decreased to negligible quantities before death but analysis of a kidney revealed large amounts in that organ. Thus, since a urine specimen free of mercury can be obtained from patients whose tissues contain the metal in appreciable quantities, a single negative result does not disprove exposure to mercury. We do not know at the present time the factors which inhibit elimination of the metal, but it is of interest that French authors[47, 62] found that after administration of sodium hyposulfite, the urine becomes free of mercury while withdrawal of the drug results in reappearance of urinary mercury. The variability of mercury elimination is in no way characteristic in acrodynia alone. Zellweger and Wehrli[95] gave to five nonacrodynic children 1 to 1.5 Gm. of calomel distributed over two to five days and examined the mercury excretion over a five-month period. In one case the elimination was determined daily from the first to the 156th day and graphically recorded. The graph shows that the amount excreted generally decreased during the first three months, but that significant amounts continued to appear from time to time in the urine. The important point is that even in the first weeks after exposure the variation in the rate of urinary excretion is enormous. For example, on the twenty-ninth day, 800 μg per liter were eliminated, but on the following day none was found in the urine. The graph demonstrates that the chances of recovering mercury from the urine are best in the first three months after exposure; but in rare instances negative findings may be obtained soon after administration of the metal and positive findings much later.[3, 47, 83, 95]

That mercury may be excreted by healthy children was pointed out in our first publication[85] and Zellweger and Wehrli[95] showed that this may be true over long periods of time and in large quantities. They found that the daily variations were similar in acrodynic and in nonacrodynic children. In no way does this speak against the mercury as the cause of acrodynia. It is well known that in chronic industrial mercurialism exposed workers may excrete large amounts of mercury but only part of them develop signs of intoxication.[1, 10, 78] Even after massive exposure within certain limits, individual susceptibility determines whether a worker becomes ill or remains well. Similarly the excretion of mercury by children indicates exposure but not necessarily disease, since only a few children exposed to small amounts of mercurial compounds become ill.

Table II also demonstrates the interesting fact that a patient may continue to excrete mercury seven months after recovery from acrodynia and remain in a state of good health. This and many a similar experience show that the metal may be in the body for a long time without causing morbid symptoms and that it often can be tolerated well after recovery from acrodynia. This tolerance corresponds to the "immunity" developed after calomel disease as described by Fanconi and associates.[37]

The marked "spontaneous" variations in elimination make it difficult to

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evaluate the effect of drugs upon excretion of the metal. Numerous authors[2, 27, 59, 61, 73, 81] have observed an increase of excretion of mercury during treatment with BAL (dimercaprol). Fischer and Hodes[39] consider administration of this drug a diagnostic measure since their patient did not excrete mercury before treatment but eliminated large amounts after initiation of therapy. In some of the cases of our present series (Cases 1, 8, 16, 21) treatment with BAL seemed to have this effect, increased elimination following administration of the drug. In other cases such results were not observed (our Cases 7, 10, 12). The patients of Bass[7] and Hutton[55] who were known to have been exposed to mercury did not excrete the metal after treatment with BAL, and Bradley and Howard's[16] patient showed a decrease after therapy. Launay and co-workers[62, 63] found evidence of a marked increase of urinary excretion of mercury after penicillin therapy was started.

Since we do not understand the mechanisms of mercurial elimination and retention in the tissues, and since we know that the daily excretion varies considerably, it is difficult to evaluate the effects of therapy. The value of determinations of mercury in the urine lies primarily in the fact that they provide proof of the patient's exposure to mercury; at times they go farther and portray the degree of severity of the exposure, particularly when the quantities found are unusually high.

In summary it may be said that exposure to mercury continues to be demonstrated in acrodynic children. If a history of exposure cannot be obtained, analysis of the urine in search for the metal should be done. *Exposure can be ruled out only if the history and repeated urinary determinations are negative.*

SYMPTOMATOLOGY OF MERCURIALISM AND ACRODYNIA

In a previous communication,[83] we emphasized the variety of adverse mercurial reactions and demonstrated that almost all the individual manifestations of acrodynia had been known long ago as manifestations of mercurialism. It is not necessary, therefore, to repeat here the review of the literature on this subject. In the past, mercury was one of the most powerful drugs in the armamentarium of the physician, and the metal was used to an extent inconceivable to the present medical generation. The earlier physicians accumulated a vast knowledge of the effects of mercurial drugs and of the state called mercurialism. In 1821 Dr. James Hamilton, Jun., Fellow of the Royal College of Physicians, and Professor of Midwifery in the University of Edinburgh, wrote a book entitled *Observation on the Use and Abuse of Mercurial Medicines in Various Diseases.*[49] It is impossible to quote here all the interesting passages pertaining to the subject, but Hamilton knew of many adverse mercurial reactions which are present in the syndrome of acrodynia. He knew that preparations of mercury "increase the action of the heart" and produce salivation, followed by emaciation and debility, and an "extremely irritable state of the whole system." The salivation, "in consequence of mercury, is accompanied with more or less local inflammation of all parts within the mouth. In some cases, besides the ordinary ulceration of the gums, and loosening and final separation of the teeth, the tongue, moveable palate, etc., swell and ulcerate to a frightful de-

gree." The erythema mercuriale was well known to him and described as follows: "This eruption is usually preceded by heat and itching of the skin, a frequent pulse, and a white tongue. . . . The parts affected are first of a faint red colour and gradually the shade becomes deeper. The eruption proceeds by slow degrees over the whole surface, accompanied with an evident tumefaction of the skin, with great tenderness and heat, and most troublesome itching . . . the cuticle loosens. . . . In some cases the hair and even the nails have also separated along with the epidermis." The description of these cutaneous reactions probably refers to acute mercurial reactions, such as those described more recently by Harper,[50] Bass,[6] and others, but Hamilton states: "The duration of the disease varies from a fortnight to eight or ten weeks, or even longer." He describes the disturbed sleep, with frightful dreams, impaired vision, frequent aches and pains in different parts of the body. "The consequences of this effect upon the nerves are different upon different subjects. In some, temporary delirium takes place—in others, palsy or epilepsy supervene, and in many the memory and judgment are more or less permanently impaired." The general impression of the condition will sound familiar to those who have cared for patients with acrodynia: "Along with all these complaints, there is such a wretchedness of look, with such a propensity to brood over their miserable feelings, that it is extremely difficult to persuade the relations or the attendants of the patient that there is no serious indisposition." Hamilton does not describe typical acrodynia, but it is very likely that he, if confronted with a case of acrodynia, would have considered the possibility of mercurialism in the differential diagnosis. The two conditions have obviously many symptoms in common. Hamilton[49] dealt with the mercurialism of the adult and the symptoms he described closely resemble the case of "Pink Disease Occurring in an Adult," reported by Doig,[34] whose patient happened to be treated with a mercurial ointment for pediculosis pubis before outbreak of the disease.

One can justifiably object that similarity of symptoms does not prove identity of two diseases and this is particularly true if there are such common symptoms as irritability, anorexia, loss of weight, polymorphic rashes and the like. But some of the manifestations which are shared by mercurialism and acrodynia are rare and more specific. Looseness and loss of apparently healthy teeth, for instance, combined with "shedding" of the alveolar processes, swelling of the gums and profuse salivation, are not everyday occurrences in human pathology; but they are characteristic of both acrodynia[11] and mercurialism.[64*] In some cases recently reported[26, 58, 69, 73, 77] as cases of acrodynia, such oral symptoms occurred and exposure to mercury could be demonstrated. Under such conditions it seems justifiable to suspect a more than casual relationship between the symptoms of mercurialism and acrodynia.

ACUTE MERCURIAL REACTIONS BECOME ACRODYNIC

The argument advanced in the preceding section can be supplemented by observations which show that a known mercurial reaction may develop into acrodynia. Harper[50] apparently

*The changes of the jaw which follow exposure to yellow phosphorus ("phossy jaw") differ distinctly from mercurial oral changes.[68]

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pointed out first that the acute idiosyncratic reactions of his patients to ammoniated mercury ointment resembled acrodynia in certain respects. In 1944 Wiedemann[87] described an acute, febrile reaction with agranulocytosis following administration of ammoniated mercury ointment. During the protracted course of the disease the author was often reminded of acrodynia, since the patient presented at times its fully developed clinical picture. The emaciated child had an unfriendly and dejected expression, the hands and feet were moist, cold, swollen and cyanotic, and the skin desquamated. The patient showed reduced motility and tremor of the hands. A comparable case was more recently reported by Williams and Beach.[90] A 3-year-old girl was treated with ammoniated mercury ointment for dermatitis of the scalp and within three days she developed a high fever and two days later, an erythematous rash. Subsequently she showed lymphadenopathy, eosinophilia, and a morbilliform rash. Within three weeks "the child's condition suggested clinical acrodynia." The patient improved rapidly under treatment with BAL. A patient of Bradley's[16] developed an acute, febrile exfoliative dermatitis following application of 5 per cent ammoniated mercury ointment. After eight days the rash subsided, the temperature returned to normal, and the patient was discharged from the hospital. The child remained anorexic and did not thrive. The hair became thin and dry and she lost her fingernails. During the following weeks she developed typical acrodynia and was readmitted to the hospital, where mercury was found in the urine. In this case, as well as in cases of Baumann[8] and Wiedemann,[88] acrodynia followed immediately after cessation of typical, acute, mercurial reactions. In two instances recorded by Fanconi and associates[37] short intervals of well-being separated the symptoms of acute mercurialism and those of acrodynia. One patient developed classical acrodynia two weeks after recovery from a febrile measles-like calomel disease. The second patient was treated for eczema with ammoniated mercury ointment and reacted with high fever and a generalized rash. Four weeks after disappearance of the acute symptoms the patient showed signs of acrodynia and eight weeks later he presented the fully developed disease picture.

These reports demonstrate that acrodynia may follow, immediately or after short intervals, acute idiosyncratic reactions to mercury.

AGE DISTRIBUTION AND MERCURIAL HABITS

There is a curious difference in the age distribution of acrodynic children reported from the British Commonwealth and those from the continent of Europe. In England and Australia, for instance, acrodynia usually occurs in infants and young children up to 2 years of age. Fisher[40] reviewing sixty-five cases in Manchester, England, records cases in early infancy. The figures rise rapidly from the age of 4 months to the end of the first year and show a sharp decline thereafter. Another report from England by Leys[65] on thirty-one patients reveals that thirty of them were under 2 years of age, the mode being at 10 months. Logan,[67] in a study of mortality from acrodynia, states that in England and Wales two-thirds of the deaths were

in children under 1 year, especially at ages 6 to 12 months. Of the other third, practically all were between the age of 1 and 2 years. The same distribution was found in a later statistical study[28] in England which showed that the great majority of deaths from pink disease occur in babies 6 months to 2 years old. In Australia, Southby[80] records the age of onset of the disease in 300 patients. His column-diagram shows that 299 of these children were under 2 years when the illness began.

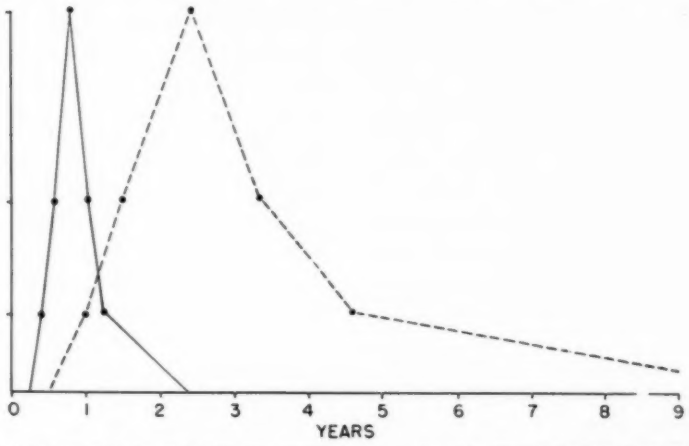

Fig. 1.—"British" age distribution curve (_____) and "Continental" age distribution curve (- - - - - -) of acrodynic children. The "British" curve is based on the column-diagram of Southby[80] and the "Continental" curve on that of Fanconi and Botsztejn[36] as described in the text.

The greatest age frequency occurred in the group 9 months old. Cheek[20] in Australia lists the ages of 136 acrodynic children of which 87 per cent were under 2 years of age. He finds it worth while to report a case of acrodynia in a child 5½ years old, since "it may not be generally realized that Swift's disease can occur after the first two or three years of life."

On the continent of Europe the situation is obviously different. In France Péhu and Boucomont[74] and Solignac[79] report the most frequent appearance of acrodynia at the ages of 3 and 4 years; that is, at an age when the disease is a rarity in England and Australia. Fanconi and Botsztejn[36] in Switzerland published a column-diagram of 101 acrodynic children observed in the Children's Hospital of Zurich. There 60 per cent of the patients were over 2 years of age!

It appeared worth while to combine the findings of Southby and those of Fanconi and Botsztejn in one graph, since they represent the "British" and the "Continental" age distributions. To this purpose we calculated from their column-diagrams means, quartiles, and the first and ninth deciles. Thus, the comparable curves of Fig. 1 were obtained. It is obvious that acrodynia befalls different age groups in these different areas and any etiologic theory of acrodynia must include this consideration.

The mercurial theory offers a satisfactory explanation, since we know the different "mercurial habits" in these areas. Reports from the British Com-

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monwealth indicate that in those countries the use of mercurial teething powders is widespread and infants and young children are exposed to the metal early. Some of them show adverse reactions, one of which is acrodynia. In Switzerland worm treatments are the "mercurial habit" and they are given to older children. It follows that acrodynia is a disease of an older age group there. Fanconi and Botsztejn[36] have also pointed out that in Switzerland calomel disease, an acute adverse reaction to mercury, and acrodynia show a similar age distribution.

In the United States the age incidence of acrodynic children is difficult to evaluate, since no statistical data on this point are available. If one considers the age of the children reported in our two series as representative, one finds the distribution intermediate between the "British" and the "Continental," the median being at 14½ months; but the third quartile is found at 2½ and the ninth decile at 3⅓ years. About 29 per cent of the acrodynic children were over 2 years old. In the United States one finds that mercurial habits vary in different areas. Teething powders are apparently limited to southern states, where calomel is also a common household remedy. The majority of the patients in our series came from the South. In northern states worm medicines and sublimate used for diaper rinses were found to be the source of mercury. Since in both the North and the South infants as well as older children are exposed to mercury, no typical regional age distribution can be expected. It must be emphasized, however, that our series is small and may not be representative of the conditions of the country.

In Cincinnati, Ohio, acrodynia is apparently a rare disease. In the Children's Hospital, a teaching hospital where rare diseases gravitate, only twenty-two cases were diagnosed as acrodynia during ten years (1941 to 1951), and the five patients seen here in the last two and one-half years, included in the present series, were sent to the hospital from communities outside of Cincinnati. The scarcity of acrodynia parallels the scarcity of positive histories of mercury ingestion obtainable in our outpatient department. The mothers of 100 children aged 1 to 2 years were asked whether they used teething powders. Only one answered in the affirmative. Many have used mercury-free teething lotions. Only one of these children had been given a worm treatment which could have contained mercury. Of sixty-five children 2 to 14 years old, five had been given anthelmintics, the contents of which could not be ascertained.

DISCUSSION

A review of the literature on acrodynia shows that the mercurial theory of its causation has been widely accepted, although there still is skepticism, particularly in areas where the disease is most frequent and where "mercurial habits" prevail.[32, 46, 57, 61, 65] This is both understandable and regrettable.

In areas where children are treated habitually for vague intestinal symptoms with calomel-containing drugs, it often seems that a child is given the medication *after* the onset of acrodynia-like symptoms; and where teething powders are widely used, it may appear that these "soothing" remedies

are administered *after* the first and nonspecific symptoms of "pink disease" began. Such an interpretation of the sequence of events is hard to refute since early symptoms of acrodynia are notoriously nonspecific and therefore present in most children at some time. How lacking in specificity such early symptoms are, can be gathered from the fact that they are said to be mistaken for teething trouble in the British areas and for worm symptoms on the continent. However, such "early symptoms" are not followed by the severe and characteristic manifestations of acrodynia unless mercurial remedies are given. Support for this viewpoint is given by the fact that in our area as in other places, many children are irritable, fretful, and salivating at the time of dentition and have complaints of abdominal pain, restless sleep, and lack of appetite later; but they are not habitually treated with mercurial remedies and their vague complaints do not develop into acrodynia. It is not likely, therefore, that the calomel given to irritable children is merely a harmless medication which coincides occasionally with the onset of acrodynia. Recent reports have also brought out the fact that healthy children may develop acrodynia following accidental exposure to mercury or after mercurial treatment for conditions which cannot be interpreted as incipient acrodynia. Thus, in Cases 3 and 21 of this series the patients were exposed to ammoniated mercury ointment which was in the house for the treatment of other members of the family. In other instances exposure occurred during play,[2, 35, 58] by routine diaper rinses,[58, 71] or by mercurial treatment for warts,[39] pediculosis pubis,[34] cerebral damage,[88] and chorioretinitis.[7] One cannot say that such patients had signs of beginning acrodynia before they were exposed to mercury.

James[57] opposes the mercurial theory on the ground that the increase in the number of cases of pink disease in the past twenty-odd years has occurred at a time when the medical use of mercury has been steadily diminishing. The fact that physicians do not prescribe mercury obviously does not protect children from exposure in other ways. The analytical results of the urine reported by James confirm the occurrence of such exposure, since not only his "pinks and atypical pinks," but also many of his control children excreted mercury. We have learned that in certain areas teething powders and worm chocolates can be bought without prescription not only in drugstores but also in groceries.

Only a few children exposed to therapeutic doses of mercury develop acrodynia or other adverse reactions. This irregular response to mercurial drugs is a well-known fact. In England in 1821, Hamilton[49] states with reference to mercurialism: "These morbid effects of mercury do not seem to depend entirely upon the quantity or mode of preparation . . . it is also notorious that very small quantities of mercury have suddenly proved equally injurious." And in modern times the capricious behavior of mercurial diuretics has been rather disturbing to those who use them frequently. Thousands of injections are given without untoward effects but occasionally a therapeutic dose results in sudden death. Only rarely is this caused by the first dose. More often the patient tolerates several—in one case 164!—doses before the fatal reaction occurs.[45] The mech-

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anism of these reactions is not clear: they can neither be explained nor predicted; yet they cannot be denied. Not only the tolerance but also the intolerance of drugs may change. We have pointed out before that in one of our cases the patient continued to excrete mercury for a long time after recovery from acrodynia, and it is known that a patient, after recovery from the disease, can be re-exposed to mercury without a relapse.[53] James[57] considers the tolerance of Mercurochrome by acrodynic children an argument against the mercurial theory. However, Bossard[14] and Fanconi and associates[37] have demonstrated that after mercurial rashes or calomel disease some children acquire a tolerance for the metal. Unfortunately, this is not always the case and other patients remain sensitive after an adverse mercurial reaction. One patient (Case 13) of our first series took a turn for the worse after Mercurochrome had been applied inadvertently to his oral lesions. Fanconi and co-workers,[37] Baumann,[8] and Laplane and collaborators[61] observed several cases of recurrent acrodynia after repeated exposure to mercury. Changes of drug tolerance to intolerance and vice versa are not limited to mercury but have been observed after administration of nirvanol, penicillin, and other drugs.

The factors which determine the intolerance for mercurial drugs are unknown. The concept of acrodynia as an allergic reaction was first developed by Helmick[51] and in recent years Fanconi and associates[37] consider the disease a neuroallergic late reaction to mercury. According to this theory only few children develop acute reactions after mercury medication, and even fewer show such late reactions as polyradiculoencephalitis, acrodynia, or lipoid nephrosis. However, the concept of acrodynia as a neuroallergic late reaction to mercury has not found general approval. It was criticized by Denys[32] because it postulates a selective sensitization of the vegetative nervous system, and because skin reactions to mercury are only rarely positive in acrodynic children. Holzel and James[53] obtained a positive patch test in only one of ten actively acrodynic patients and found no increased incidence of allergic disorders in their patients compared to the general child population. Ivady and co-workers[56] found no proof of allergy in their cases of acrodynia. However, Daisley and associates,[27] Mayer,[69] Gobbi,[44] and Bakx and collaborators[4] contribute data which favor the assumption that children who incline to allergic reactions have an increased tendency to develop acrodynia.

Allergy can be defined as an alteration in reactivity resulting from exposure to an exciting agent and manifested upon *re-exposure* to the same agent.[31] While some cases of acrodynia begin after re-exposure to mercury, others commence many weeks or even months after administration of a mercurial drug and without apparent re-exposure. This behavior, known long ago as a characteristic of mercurialism,[49, 64] cannot be called an allergic reaction. Urinary excretion studies of mercury appear to have demonstrated that the organism can harbor appreciable amounts of mercury while maintaining perfect health, and then, for unknown reasons, these innocuous stores of mercury become toxic. It seems in such cases as if the barriers which held the mercury in check break down without provocation, or as if the

mercury had been converted from a nontoxic into a toxic form.

No useful purpose would be served here by arguing the merits of various interpretations of the hypersensitivity which is observed, but it is important to find the factors which render useful mercurial drugs dangerous to some individuals at certain times, in order to learn to predict and prevent these rare complications.

A review of recent publications does not show that acrodynic patients have had any experience in common besides exposure to mercury. The case of Daisley and associates[27] is of interest because their patient underwent a fourteen-day course of antirabies injections six weeks before outbreak of acrodynia. Ten days after completion of the preventive therapy she was treated with ammoniated mercury ointment and subsequently acrodynia developed. Ten other patients received the antirabies treatments at the same time as the patient but none of these suffered a reaction. In Hutton's case[55] antirabies treatment preceded the onset of the disease by three months. In several children of our series and in some recently reported, various immunization procedures preceded the onset of acrodynia in addition to mercurial exposure. This could be purely coincidental or the vaccination material may play a role as an accessory factor. It is noteworthy that many vaccines and sera contain small amounts of mercury as preservatives which are injected together with the biologic material. These small amounts of mercurial compounds, which enter the body unnoticed, could act as sensitizing substances. This fact should be kept in mind in the analysis of future cases of acrodynia. In several instances vaccination against smallpox preceded the development of acrodynic symptoms, and some patients were exposed to bismuth, arsenic, lead, and antimony in addition to mercury.[2, 25, 58] Such observations deserve attention, but so far the results are too heterogenous to account for the secondary factors needed for a complete understanding of the etiology of acrodynia.

The revived theory of adrenal insufficiency by Cheek and co-workers[21-24] has also failed to reveal the "nature, prevention and cure of acrodynia." This theory cannot be discussed here, since it has become rather complicated, and since not all the findings on which it is based could be confirmed.[76, 91] It should be pointed out, however, that neither the findings of a disturbed electrolyte balance nor those of other physiologic constants of the blood are in conflict with the mercurial theory. By elucidation of the pathologic physiology of acrodynia valuable contributions can be made to a better understanding of mercurialism.

Acrodynia, although a rare disease, has held the interest of pediatricians for the last thirty years. The fact that the disease usually lasts for several months and that it subjects not only the affected child but the entire family to suffering may account in part for this interest. The recovery is not always complete and residual neurological defects and behavior problems have been observed.[53, 74] The mortality is over 10 per cent[20, 53] and in England 585 deaths were ascribed to pink disease from 1939 to 1948.[28] But in addition to these practical considerations, there existed an interest in this disease because of the difficulty in explaining and in clarifying it. The discovery of mercury as the most frequent causa-

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tive agent of the acrodynic syndrome coincides with a general increased interest in poisons as a cause of diseases in children. With the advent of powerful drugs used against microorganisms, the study of their toxic side effects emerges as a major medical problem.[19] The fact that drugs, tolerated by the majority of patients, can be dangerous to a few, cannot be ignored, and methods must be found to protect those who may be harmed by doses therapeutic to others. For this reason, the questions raised by Fanconi and his co-workers[37] concerning allergy, "immunity," and skin tests to mercury are of general significance and extend beyond the sphere of acrodynia.

Intolerance to mercury in the form of acrodynia has features which differ from other drug reactions. Since the metal can be stored in the body to some extent and intolerance may develop long after exposure, morbid symptoms may appear weeks or months after the child has been given the injurious drug. This late effect makes mercurial drugs treacherous, since the cause of the ill effects escapes recognition. The deleterious effects of relatively small doses of mercury upon the nervous system, which are seen sometimes in the course of acrodynia, add to the peculiarity of the "acrodynic reaction." We have already pointed out[83] that acrodynic reactions can be brought about in exceptional cases by toxic substances other than mercury. We mentioned arsenic and gold, and Wiedemann[88] added thallium to the list. The latter poison causes rashes, pruritus, perspiration, loss of hair, tachycardia, hypertension, and hypotonia, symptoms which certainly are suggestive of acrodynia. In the older literature it was asserted repeatedly that acrodynic symptoms may appear in the course of poliomyelitis.[70, 74] Such atypical cases of poliomyelitis may have been confused occasionally with neurological complications of acrodynia, and exposure to mercury was not excluded at that time. However, recently Zellweger[94] re-emphasized that acrodynia can occur during or after paralytic poliomyelitis and in association with other organic diseases of the brain. If this is the case, one cannot expect a complete eradication of acrodynia by withholding mercurial compounds from children.

The mercurial theory of acrodynia has effected a change in the delineation of the clinical concept of this disease. The nature of abortive cases can now be recognized by the proof of exposure to mercury. Protracted and subacute mercurial reactions with acrodynic signs can be included among the "atypical" cases. Some morbilliform and scarlatiniform prodromal exanthemas or megaloerythema, which were formerly mistaken for infectious diseases and causes of acrodynia, are now recognized as toxic mercurial rashes or calomel disease.[37] The Guillain-Barré syndrome has been known as a complication of acrodynia for some time.[29, 68] Later it was shown that "polyradiculitis" without acrodynia may follow mercurial worm treatments[37] or application of a mercurial ointment[42]; and in a previous communication[83] we cited a case of acrodynia complicated by the Guillain-Barré syndrome which had been brought on by mercurial diaper rinse (Case 27). Similarly, a link was established between acrodynia and certain cases of lipoid nephrosis which may follow the administration of calomel.

Fanconi and associates[37] described two cases of benign nephrosis which followed worm treatment with calomel. Later Holzel and James[53] in a study of mercury and pink disease encountered three cases of nephrosis in young children who had been given mercurial teething powders and were excreting significant amounts of mercury in the urine. One of these children also had typical acrodynia while in two others the syndrome was incomplete. This led to a study by Wilson and co-workers[92] on mercury nephrosis in young children following ingestion of mercurial teething powders. These examples show new facets in the syndrome of acrodynia, which are understandable if one considers their common mercurial origin.

Treatment with BAL as recommended by Bivings and Lewis[13] has been practiced in many recent cases of acrodynia. In 1950 Bivings reviewed the results of treatment of fifty-one acrodynic children.[12] Of these, twenty-nine recovered rapidly, twelve recovered gradually, six recovered slowly, one failed to respond, and three died. In our present series eighteen patients were treated with BAL. Of these, four patients recovered rapidly, eight gradually, three slowly; the outcome was unknown in three cases. There were no deaths. In recent publications rapid recovery after BAL therapy was reported by Andersen,[2] Bakx and collaborators,[4] Bancroft and co-workers,[5] v. Creveld,[81] Hutton,[55] Ivady and associates,[56] Kirk,[58] Peeters,[73] and Williams and Beach[90]; gradual improvement by Bass,[7] Bradley and Howard,[16] Daisley and associates,[27] Fischer and Hodes,[39] Frankel,[41] Holzel and James,[53] Laplane and co-workers,[61] McCoy,[71] and Silverman and Cassady[77]; and no response by Denys[32] and Laplane and associates (Case 2).[61] It is not clear why some patients show dramatic improvement while others fail to respond. Long duration of the disease before the institution of treatment with BAL may account for some of the failures,[32] but in other instances rapid recovery ensued, although the intervals between onset of symptoms and treatment were several months.[2, 55, 58] Adverse reactions to BAL were mentioned by Bivings,[12] Beale and Schrum,[9] and Daisley and collaborators.[27]

Launay and associates[63] recommended treatment of acrodynia with penicillin, since they observed an increased elimination of mercury after administration of this drug. In some cases this treatment seemed to be successful[15, 61, 63] but it failed in others.[15, 25, our Case 2]

It would appear that sufficient evidence has been accumulated to demonstrate that relatively small amounts of mercury can produce acrodynia and associated disorders. It is to be hoped that the mercurial theory will be tested soon in areas where acrodynia is endemic by a concerted effort of physicians, druggists, and manufacturers of unnecessary mercurial preparations.[96] If teething powders must be given, there is no need to add mercury to them. Teething lotions free of mercury seem to be just as effective in soothing mothers and children as the potentially dangerous preparations. The same holds for the habitual treatment of vague complaints by mercurial worm treatments. Even when intestinal parasites are found, it is not necessary to prescribe calomel. Fanconi and Morf,[38] discussing ascariasis, stressed the dangers of treatment with

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mercurial preparations, and we suggested that santonin and mild mercurous chloride and other vermifuges containing mild mercurous chloride can be replaced by more effective agents.[83] This suggestion is apparently not new, since Hamilton in 1821 came to similar conclusions[49]: "Mercurial anthelmintics being thus dangerous, it is obvious that their use could be sanctioned on the principle of necessity, viz. that no other equally efficacious medicines for the expulsion of worms were known. Fortunately, however, this is not the case, as there are many different articles of the materia medica which possess the same vermifuge power, and are perfectly safe in their operation." It remains to be seen whether this admonition will be heeded after a lapse of 131 years.

We have discussed in this review some adverse and serious reactions to mercurial drugs and suggested that their indiscriminate use be abandoned. Since mercurial compounds can be very harmful to some children, their use as household remedies should not be tolerated. Also they should not be used routinely by physicians. However, many mercurial drugs are effective when used judiciously, and they should not be discarded. Some of the modern drugs which have replaced mercury in recent years also produce deleterious side effects[17, 19] and their comparative risks have yet to be evaluated.

SUMMARY

A series of twenty-eight new cases of acrodynia is reported. In all cases exposure to mercury could be demonstrated by history or by urinalysis. The recent literature on mercury, and acrodynia and related diseases is reviewed and discussed.

REFERENCES

1. Agate, J. N., and Buckell, M.: Mercury Poisoning From Fingerprint Photography; Occupational Hazard of Policemen, Lancet 2: 451, 1949.
2. Andersen, B.: Acrodynia Caused by Exposure to Mercury, J. Oslo City Hosp. 1: 161, 1951.
3. Armaingaud: Présence de Mercure dans les Urines des Acrodyniques, Pédiatrie 4: 645, 1949.
4. Bakx, C. J. A., Lingeman, J., and Peters, H. J.: Kwikvergiftiging als Oorzaak van Acrodynie, Nederl. tijdschr. geneesk. 95: 378, 1951.
5. Bancroft, P. M., Grant, R. S., and Tanner, F. H.: Acrodynia Associated With Mercury Poisoning, Journal-Lancet 71: 56, 1951.
6. Bass, M. H.: Idiosyncrasy to Ammoniated Mercury Ointment in Childhood, Urol. & Cutan. Rev. 45: 78, 1941.
7. Bass, M. H.: L'Idiosyncrasie du Mercure Pendant l'Enfance, Arch. franç. pédiat. 8: 709, 1951.
8. Baumann, T.: Calomel-Krankheiten: Ein allergisches Krankheitsbild, Schweiz. med. Wchnschr. 79: 725, 750, 1949.
9. Beale, J. D., Jr., and Schrum, D. I.: Serious Toxic Reaction Associated With Administration of BAL, J. PEDIAT. 35: 498, 1949.
10. Bidstrup, P. L., Bonnell, J. A., Harvey, D. G., and Locket, S.: Chronic Mercury Poisoning in Men Repairing Direct-Current Meters, Lancet 2: 856, 1951.
11. Bilderback, J. B.: Acrodynia, in Brennemann, J.: Practice of Pediatrics, Hagerstown, Md., 1948, W. F. Prior Co., Inc., Vol. 4, chap. 20.
12. Bivings, L.: Treatment of Acrodynia With BAL, Tr. Sixth Internat. Cong. Pediat. Zurich, Summaries of Communications and Discussions, p. 213, 1950.
13. Bivings, L., and Lewis, G.: Acrodynia; a New Treatment With BAL, J. PEDIAT. 32: 63, 1948.
14. Bossard, G.: Ueber seltene Formen der Quecksilbervergiftung mit besonderer Berücksichtigung der Exantheme nach innerlicher Anwendung, Dermat. Ztschr. 4: 50, 1897.
15. Bouineau, M.: Quatre cas d'Acrodynie Traités par la Pénicilline, Arch. franç. Pédiat. 8: 785, 1951.
16. Bradley, J. E., and Howard, A.: Acrodynia: A Report of a Case Treated With BAL, Bull. School Med. Univ. Maryland 35: 113, 1950.
17. Brown, E. A.: Progress in Allergy; Reactions to Penicillin; Review of Literature, 1943-1948, Ann. Allergy 6: 723, 1948.
18. Carithers, H. A.: Mercury Poisoning Producing Subacute Acrodynia and Its Treatment With Dimercaprol, Pediatrics 4: 820, 1949.

19. Carr, E. A.: Allergy to Drugs, New England J. Med. **245:** 892, 935, 1951.
20. Cheek, D.: Report of a Case of Swift's Disease in a Child Aged Five-and-a-half Years, Clin. Rep. Adelaide Children's Hosp. **1:** 209, 1949.
21. Cheek, D. B.: Pink Disease: an Investigation of Its Cause and Treatment, M. J. Australia **1:** 101, 1950.
22. Cheek, D. B.: Pink Disease: the Manifestation in Older Children and the Estimation of the Blood Adrenaline Content, M. J. Australia **1:** 353, 1951.
23. Cheek, D. B., and Hicks, C. S.: Pink Disease or Infantile Acrodynia; Its Nature, Prevention and Cure, M. J. Australia **1:** 107, 1950.
24. Cheek, D. B., Hetzel, B. S., and Hine, D. C.: Evidence of Adrenal Cortical Function in Pink Disease, M. J. Australia **2:** 6, 1951.
25. Corcos, A., Stam'rad, M., and Abitrol, S.: Un cas Mortel d'Acrodynie Mutilante chez un Enfant de 5 ans Traité par un derivé Mercuriel, Arch. franç. pédiat. **8:** 311, 1951.
26. Corcos, V.: Acrodynie chez une Enfant de 18 mois Traitée 3 mois Auparavant par des Frictions Mercurielles et dont les Urines Contenaient du Mercure, Arch. franç. pédiat. **6:** 432, 1949.
27. Daisley, G. W., Clark, H., and McLendon, P. A.: Report of a Case of Acrodynia Treated With BAL, Clin. Proc. Child. Hosp. **7:** 178, 1951.
28. Death From Pink Disease, Brit. M. J. **1:** 366, 1951.
29. Debré, R., Marie, J., and Messimy: Forme Quadriplégique de l'Acrodynie, Bull. et mém. soc. méd. Hôp. Paris **50:** 1075, 1934.
30. Debré, R., Schapira, G., and Royer, S.: Acrodynie et Hydrargyrurie, Arch. franç. pédiat. **9:** 443, 1952.
31. Definitions of Words Pertaining to Allergy, by the Committee on Nomenclature for the Association of Allergy Clinics of Greater New York, J. Allergy **12:** 202, 1941.
32. Denys, P.: Acrodynie, Mercure et B.A.L., Acta paediat. belg. **4:** 16, 1950.
33. Desarmenien, H. F.: Contribution à l'étude du Rôle Etiologique du Mercure dans l'Acrodynie, Paris, 1950.
34. Doig, K. M.: Pink Disease Occurring in an Adult, M. J. Australia **1:** 782, 1938.
35. Esp, E.: Infantil akrodyni, Tidsskr. norske laegefor. **70:** 266, 1950.
36. Fanconi, G., and Botsztejn, A.: Die Feersche Krankheit (Akrodynie) und Quecksilbermedikation, Helvet. paediat. Acta **3:** 264, 1948.
37. Fanconi, G., Botsztejn, A., and Schenker, P.: Ueberempfindlichkeitreaktionen auf Quecksilbermedikation im Kindesalter mit bedonderer Berücksichtigung der Calomelkrankheit, Helvet. paediat. Acta (supp. 4) **2:** 3, 1947.
38. Fanconi, G., and Morf, H.: Die Askaridiasis und ihre Behandlung, Gefahren der Kuren mit Quecksilberpräparaten, Praxis (Bern) **38:** 903, 1949.
39. Fischer, A. E., and Hodes, H. L.: Subacute Mercury Poisoning (Acrodynia) Caused by Protiodide of Mercury, J. PEDIAT. **40:** 143, 1952.
40. Fisher, T. N.: Pink Disease; Review of 65 Cases, Brit. M. J. **1:** 251, 1947.
41. Frankel, E.: Mercury and Pink Disease, Lancet **1:** 611, 1952.
42. Gabinus, O., and Pöldre, A.: Polyradiculitis—ett Neuroallergiskt Syndrom, Nord. Med. **45:** 723, 1951.
43. Glanzmann, E.: Studien für Selter-Swift-Feerschen Krankheit, Volume jubilaire en l'honneur de M. L. Dapples, Vevey, 1937, p. 173.
44. Gobbi, V.: Considerazioni su alcuni casi di Acrodinia, Clin. Pediat. **31:** 664, 1949.
45. Gottlieb, P. M.: Sensitivity to Mercurial Diuretics; Report of a Case of Urticaria Due to Mercupurin, Ann. Allergy **6:** 518, 1948.
46. Griffith, G.: Pink Disease; Review of 27 Cases, Edinburgh M. J. **57:** 162, 1950.
47. Hadengue, A., Fabiani, P., and Queuille, A.: Note sur l'Elimination Urinaire du Mercure, Arch. mal. profess. **11:** 45, 1950.
48. Hamilton, A., and Hardy, H. L.: Industrial Toxicology, New York, 1949, Paul B. Hoeber, Inc.
49. Hamilton, J.: Observations on the Use and Abuse of Mercurial Medicines in Various Diseases, New York, 1821, E. Bliss & E. White.
50. Harper, P.: Idiosynerasy to Ammoniated Mercury Ointment; Report of 2 Cases, J. PEDIAT. **5:** 794, 1934.
51. Helmick, A. C.: Symptomatology of Acrodynia as a Basis for a New Line of Investigation as to Its Etiology, Arch. Pediat. **44:** 405, 1927.
52. Hengeveld, F. M. C.: Acrodynie behandeld met BAL, Nederl. tijdschr. geneesk. **95:** 2025, 1951.
53. Holzel, A., and James, T.: Mercury and Pink Disease, Lancet **1:** 441, 1952.
54. Houet, R.: Report of Two Cases of Acrodynia Appearing After Calomel Therapy But Without Excretion of Mercury in the Urine and Cured With BAL, Acta paediat. **41:** 158, 1952.
55. Hutton, P. W.: Case of Acrodynia (Pink Disease) Treated With Dimercaptopropanol (BAL), East African M. J. **26:** 263, 1949.
56. Ivady, G., Horvai, R., and Timar, A.: Contribution to the Problem of Acrodynia and Mercury, Gyermekgÿógyázat (Budapest) **2:** 87, 1951.
57. James, G. A.: Mercury as a Cause of Pink Disease, Great Ormond St. J. **1:** 48, 1951.
58. Kirk, T. R.: Dimercaprol in the Treatment of Acrodynia, J. Michigan M. Soc. **50:** 739, 744, 1951.

UNIVERSITY OF MICHIGAN LIBRARIES

59. Kromann, B.: Acrodynia: a Review and Report of a Case, with Mercury in the Urine, Cured Following Treatment with Dimercaprol, Ugesk. laeger. **112**: 925, 1950.
60. Kühl, G.: Zur Pathogenese der Feerschen Neurose des vegetativen Systems im Kindesalter, Ztschr. f. Kinderh. **45**: 315, 1927.
61. Laplane, R., Fabiani, P., and Desarmenien, H.: Acrodynie et Mercure, Nourrisson **39**: 235, 1951.
62. Launay, C., Fabiani, P., Grenet, P., Hadengue, A., and Radzievsky: Absorption massive et prolongée de Calomel chez un Enfant. Etude de l'Élimination du Mercure, Arch. franç. pédiat. **7**: 75, 1950.
63. Launay, C., Fabiani, P., Grenet, P., Hadengue, A., Solignac, and Strauss: Un nouveau Cas d'Acrodynie avec Présence de Mercure dans les Urines, Arch. franç. pédiat. **7**: 79, 1950.
64. Lewin, L.: Die Nebenwirkungen der Arzneimittel, Berlin, 1893, A. Hirschwald.
65. Leys, D.: Review of Infantile Acrodynia (Pink Disease), Arch. Dis. Childhood **25**: 302, 1950.
66. Leys, D.: Teething Powders, Lancet **2**: 1053, 1949.
67. Logan, W. P. D.: Mortality From Pink Disease in 1923-1947, Lancet **1**: 608, 1949.
68. Marie, J.: L'acrodynie paralytique grave avec Dissociation Albumino-cytologique du Liquide Rachidien, Arch. franç. pédiat. **1**: 217, 1943.
69. Mayer, M.: Zur Aetiologie der Feer'schen Krankheit, Arch. f. Kinderh. **144**: 58, 1952.
70. Mayerhofer, E.: Atypische Poliomyelitiden und deren ätiologische Beziehung zur infantilen Acrodynie, Ann. paediat. **153**: 144, 1939.
71. McCoy, G. E.: Acrodynia Following Use of Bichloride of Mercury Diaper Rinse: Report of 2 Cases, J. Indiana M. A. **43**: 1095, 1950.
72. Morhardt, P. E.: Acrodynie et Intoxication par le Mercure, Concours Méd. **72**: 3539, 1950.
73. Peeters, R.: Trois formes d'Intoxication Mercurielle, Acta paediat. belg. **4**: 233, 1950.
74. Péhu, M., and Boucomont, J.: L'acrodynie Infantile, Paris, 1944, Masson et Cie.
75. Peluffo, E., and Vignale, R.: Acrodinia Intoxicación Mercurial y B.A.L., Arch. Pediat. Uruguay **22**: 803, 1951.
76. Pink Disease, Lancet **1**: 1216, 1951.
77. Silverman, F. N., and Cassady, H. A.: Acrodynia Following Ingestion of Mercurial Ointment; Late Dental Sequella, New England J. Med. **247**: 343, 1952.
78. Smith, A. R., and Moskowitz, S.: Urinary Excretion of Mercury, N. Y. State Dept. of Labor, Month Rev. **27**: 45, 1948.
79. Solignac, H.: Acrodynie Infantile, France Méd. **13**: 14, 1950.
80. Southby, R.: Pink Disease with Clinical Approach to Possible Etiology, M. J. Australia **2**: 801, 1949.
81. van Creveld, S., and Paulssen, M. M. P.: Acrodynia and Mercury Poisoning, Acta paediat. **38**: 82, 1949.
82. Warkany, J.: Mercury and Acrodynia, Tr. Sixth Internat. Cong. Pediat., Summaries of Communications and Discussions, Zurich, p. 212, 1950.
83. Warkany, J., and Hubbard, D. M.: Adverse Mercurial Reactions in the Form of Acrodynia and Related Conditions, Am. J. Dis. Child. **81**: 335 1951.
84. Warkany, J., and Hubbard, D. M.: Mercury in the Urine of Children With Acrodynia, Am. J. Dis. Child. **79**: 388, 1950.
85. Warkany, J., and Hubbard, D. M.: Mercury in the Urine of Children With Acrodynia, Lancet **1**: 829, 1948.
86. Watkins, C. G.: Etiology and Treatment of Acrodynia With Report of 7 Cases, North Carolina M. J. **11**: 188, 1950.
87. Wiedemann, H. R.: Quecksilbervergiftung mit Agranulozytose bei einem Kleinkinde, Arch. f. Kinderh. **132**: 127, 1944.
88. Wiedemann, H. R.: Zur Feerschen Krankheit, Med. Klin. **44**: 1433, 1949.
89. Wiedemann, H. R.: Zur Feerschen Krankheit, Monatschr. f. Kinderh. **97**: 357, 1949.
90. Williams, B. H., and Beach, W. C.: Idiosyncrasy to Ammoniated Mercury; Treatment With 2,3-Dimercaptopropanol (BAL), J. A. M. A. **142**: 1286, 1950.
91. Williams, H., MacDonald, W. B., and Callow, V.: Pink Disease: Its Relation to Adrenal Function and the Value of Salt and Desoxycorticosterone in Treatment, M. J. Australia **1**: 363, 1951.
92. Wilson, V. K., Thomson, M. L., and Holzel, A.: Mercury Nephrosis in Young Children With Special Reference to Teething Powders Containing Mercury, Brit. M. J. **1**: 358, 1952.
93. Zellweger, H.: Feersche Krankheit und Quecksilber, Schweiz. med. Wchnschr. **80**: 1194, 1950.
94. Zellweger, H.: Neurovegetative Störungen bei Poliomyelitis. I. Störungen bedingt durch die Affektion der autonomen Zentrum im Hirnstamm, Helvet. paediat. acta **5**: 195, 1950.
95. Zellweger, H., and Wehrli, S.: Der Quecksilbernachweis im Urin und seine Bedeutung für die Diagnose der Akrodynie, Helvet. paediat. acta **6**: 397, 1951.
96. Baumann, Th.: Zur Frage der Häufigkeit der Sensibilisierung durch Quecksilber als Ursache der infantilen Akrodynie, Schweiz. med. Wchnschr. **82**: 375, 1952.
97. Najman, E., and Četkovič, S.: Beitrag zur Frage der Aetiologie der Akrodynie infolge Quecksilberüberempfindlichkeit, Ann. pediat. **179**: 81, 1952.

Psychologic Aspects of Pediatrics

JUVENILE DELINQUENCY

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THE term delinquency refers to repeated acts, committed by a juvenile, of a kind which, if they were committed by an adult, would be punishable as crimes. This definition excludes children who occasionally come into conflict with the law. Petty crimes, for example, pilfering, are so widespread among children as to be considered a part of the normal developmental process.

Delinquency is increasing. Court statistics, gathered by the Children's Bureau, show a rise of 19 per cent in the cases handled by the courts in the United States between 1948 and 1951. Approximately 350,000 children come before the juvenile courts each year. In certain years as many as one-third of the persons arrested for automobile theft and for breaking and entering are juveniles (aged 10 to 17 years). It is significant that less densely populated areas (population less than 100,000) are experiencing even sharper increases than the larger communities.

When a juvenile is apprehended by the police for a delinquent act he may be dismissed with a warning, placed in the custody of his parents, or detained for a court hearing. About one-fourth of the juvenile lawbreakers are referred to court. Once in court the youngster may be discharged, placed on probation, or committed to a training school or some other type of foster care.

In 1950 Sheldon and Eleanor Glueck of Boston reported a comparative study of 500 delinquent and 500 nondelinquent boys. The boys varied in age from 11 to 17 years and were matched for age, ethnic origin, and general intelligence. The children of both groups lived in poverty or near-poverty and resided in underprivileged urban neighborhoods. The Gluecks' report gives a clear picture of the various aspects of the delinquent boy.

One of the most significant facts brought out by their studies is the early age at which delinquents begin to get into trouble. In many, difficulties such as disobedience, unruliness, defiance, stubborness, temper tantrums, begin in kindergarten or first grade. Nearly half of the delinquents studied by the Boston workers were in some trouble before their eighth year and another two-fifths before their eleventh year.

Though normal boys frequently commit minor transgressions such as hopping trucks, petty pilfering, occasional truancy, and smoking, delinquents generally give a history of persistent and serious misbehavior such as burglary, various forms of larceny, automobile theft, crimes against the

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public order, running away, truancy, assault and battery, and the like. Court appearances and convictions take place early (average age 12.4 years) and are repeated.

In their emotional attitudes the lawbreakers tend to be hostile, defiant, resentful, suspicious, socially assertive. They have a strong feeling that they are not being appreciated. In addition they tend to be parasitic, desiring to be looked after without their making efforts on their own behalf, and they have a strong desire for power and position. Their behavior is on the whole uncooperative, unconventional, nonsubmissive to authority, independent, and uninhibited. Other traits are stubborness, egocentricity, lack of self-criticism, sensuality. Their social, sexual and family relationships are less satisfactory than those of law-abiding boys. Conflicts are often expressed in action, sometimes in feeling, rather than being suppressed or bottled up as in the case of other individuals. On the other hand they suffer less than normals from such emotional attitudes as anxiety, feelings of insecurity, helplessness and powerlessness, fear of failure and defeat. Healy and Bronner emphasize that the delinquent is a dissatisfied person.

The school performance of delinquent boys is, in general, poorer than one would expect from their intelligence level. They tend to be uninterested, inattentive, careless, lazy, and are frequently left behind. They have little if any drive for formal training of any sort and give little thought to planning for the future. They misbehave frequently at school. The after-school jobs which they select are principally street trades such as peddling, boot blacking, and selling newspapers and less often jobs such as office workers or store helpers where they are subject to a certain amount of supervision and protection.

As leisure time pursuits delinquent boys generally seek adventurous activities rather than competitive sports or games or quiet amusements. The activities chosen are stealing rides, hopping trucks, roaming the streets after dark, smoking and drinking at an early age, destructive mischief, running away, firesetting, gambling. The greater thirst for excitement is further expressed in their excessive attendance at movies.

ETIOLOGY

Students of the subject are agreed that the factors which make a child delinquent are many and varied. No single cause can be found. The following factors, though not operative in every case, are found in higher proportion among delinquent than nondelinquent children.

Physique. According to the Gluecks, delinquent boys as a group are sturdier, more masculine, and more muscular than nondelinquents. Bodily disproportions are less frequent.

Family background. The family backgrounds of delinquent boys are, by and large, inferior to those of law-abiding boys from the same socioeconomic environment. The incidence of emotional disturbance, mental retardation, alcoholism, and criminal behavior is likely to be high. The parents show less effort to set up decent standards of conduct for their children, are less ambitious for themselves and their offspring, do little planning for the future, and are on the whole less self-respecting.

The homes are often unstable and are frequently broken by separation, divorce, death, or prolonged absence of one of the parents. A warm emotional tie between parents and child is unusual. The mothers tends to be lax and to pay little attention to the boys' misbehavior. They are often inconsistent in their disciplinary attitudes. The fathers, on the other hand, are more often overstrict and resort frequently to physical punishment. The families change their residence frequently so that the boys have little chance of establishing neighborhood ties.

The parents may be characterized as showing little understanding, affection, stability, or moral fiber and as being generally unfit to be proper guides and protectors or suitable objects of respect for their children.

It would appear that certain children are so constituted as to make them more susceptible to influences leading to delinquency. The Gluecks point to a temperament which is restlessly energetic, impulsive, extroverted, aggressive, destructive; an attitude which is hostile, defiant, resentful, suspicious, stubborn, socially assertive, adventurous, unconventional, nonsubmissive or ambivalent to authority; an intellect which tends to direct concrete rather than symbolic and abstract expression and which lacks a methodical approach to problems.

An important factor, which may explain in part at least the current increase in delinquency, is the dwindling ability of church, state, and community to influence the individual to behave in accord with the will of the group as a whole (Tappan, 1949). As moral and conventional norms are losing their force, more and more of the responsibility for control has been shifted to the state and its courts and these have proved to be ineffectual in curbing lawless behavior.

The following have been found to be of little or no influence in leading to delinquent behavior:

The health status of delinquent differs in no essential way from that of law abiders.

Economic status. Poverty does not appear to be a prominent factor leading to delinquency. Nor do conditions of prosperity reduce delinquency. It is true that the delinquency rate rose somewhat during the depression years 1929 to 1933 but the rate rose much more sharply and to a much higher level than ever before in 1943 and has continued to increase ever since. Extensive slum clearance since the war has also been without beneficial effect.

Intelligence. The proportion of feeble-minded among delinquents is somewhat higher than in the general population. This is due, in part at least, to the greater likelihood that the defective will be more readily apprehended. The proportion of mental defectives that are delinquent is small. The average I.Q. of lawbreakers is not far below average.

Membership in gangs has been given a prominent place in the etiology of delinquency. The findings of the Gluecks do not bear this out. Though over half the lawbreakers in their study group joined gangs, in contrast to only 0.6 per cent of the nondelinquents, the delinquents revealed their antisocial behavior long before they became gang members. "Gang membership may have multiplied their antisocial activities, it rarely originated persistent delinquency."

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Conflicts between a foreign culture of the parents and their American-born sons, often considered a prominent factor in bringing about delinquent behavior, was of no influence in the group studied by the Gluecks, the proportion of foreign-born parents being the same in the delinquent and nondelinquent groups.

Psychiatric disorders. Neither the psychoneuroses nor the psychoses appear to play a prominent part in the etiology of delinquency. According to the Gluecks the psychopathic personality is rarely found in delinquents. Neuroticism is also unusual but a number of isolated neurotic symptoms are found frequently in delinquents—compulsions, need for self-punishment, symbolic expression of repressed urges, aggression, feeling of being abandoned, adventurousness, suggestibility, stubbornness, conflicts arising out of an inability to adjust to the family and out of problems related to sexual identification.

Regarding the relation of play activities to delinquency Tappan considers that the following generalizations are fairly clear:

"1. Being a good athlete is no deterrent at all to delinquency.

"2. Experience in team play through recreation can have no significant amount of carry-over to general character traits or conduct patterns.

"3. Even highly organized recreational activities do not absorb enough of the energy or time of a child to reduce appreciably his opportunities to engage in delinquency.

"4. In fact a play group may itself help to stimulate its member to illegal activities, engaged in 'for fun' after their games are over; the probability of this is increased when delinquent or near-delinquent members are in the group.

"5. Many of the recreational programs do not in any event reach those children who are presumed to need the most because of their problems of health or delinquency.

"6. If a child is disposed toward law violation it will require much more than games and sports to do anything effective about it.

"7. Where children have come to enjoy their delinquencies as games—so commonly the case—the thrills thus provided are usually greater than those which organized recreation can provide. The latter can be urged as a substitute not for their intrinsic competitive appeal, where they are at a disadvantage, but only on social and moral grounds."

PREVENTION

As yet, no effective means of preventing delinquency has been discovered. The idea of Dr. Richard Cabot that supplying the "predelinquent" boy with an adult "friend" who would stand by him through thick and thin and who would make available to him the opportunities and moral guidance that parents normally supply was tested by Powers and Witmer and found to be effective only occasionally in preventing future misbehavior.

The Gluecks propose an integrated approach to the problem through the individual himself, the family, the school, and leisure-time pursuits. They would submit children to early and repeated personality examination in order to detect distortions of emotional development at a stage when it might be possible to effect changes. Family

counselling might help to avoid and correct some of the evidences of disruption in the home. The school needs a more individual and personal attitude. As for leisure-time pursuits, settlement houses, school community centers, church centers, boys' clubs, and the like must take into account the preferences of these adventure-loving boys who dislike supervision.

REFERENCES

Burt, C. L.: The Young Delinquent, ed. 4, London, 1944, University of London Press.

Bovet, L.: Psychiatric Aspects of Juvenile Delinquency; World Health Organization, Monograph Series No. 1, Geneva, 1951.

Glueck, S., and Glueck, E. T.: Delinquents in the Making, Paths to Prevention, New York, 1952, Harper and Brothers.

Ibid.: Unraveling Juvenile Delinquency, New York, 1950, The Commonwealth Fund.

Healy, W., and Bronner, A. F.: What Makes a Child Delinquent? Forty-seventh Yearbook of the National Society for Study Education, Chicago, 1948, University of Chicago Press, p. 30.

Powers, E., and Witmer, H.: An Experiment in the Prevention of Delinquency, New York, 1951, Columbia University Press.

Tappan, P. W.: Juvenile Delinquency, New York, 1949, McGraw-Hill Book Co.

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Comments on Current Literature

THE USE OF HYALURONIDASE IN THE TREATMENT OF ACUTE HEMOPHILIC HEMARTHROSIS

THE enzyme, hyaluronidase, produced commercially as an organic tissue extract from the gonads of bulls, has been used to advantage in a number of clinical conditions. This enzyme is capable of depolymerizing and hydrolyzing hyaluronic acid, a mucopolysaccharide which constitutes the chief component of ground substance, is present as a gel in intercellular substance, and which is known to occur in body fluids such as vitreous humor and synovial fluid. The fundamental mechanism of action of hyaluronidase lies in its power to decrease viscosity and increase permeability, which brings about a freer flow of fluid through intercellular spaces. Likewise, where there is greater dispersion, areas for fluid absorption are extended.[1]

At the suggestion of Britton and Habif,[2] who noted that hyaluronidase can hasten the absorption of blood from a joint, MacAusland and Gartland[1] have made use of this physiologic principle by employing the enzyme in the treatment of hemophilic patients who develop hemarthrosis. In a report which appeared in one of the November, 1952, issues of the *New England Journal of Medicine,* MacAusland and Gartland review their experience with the treatment of hemarthrosis in six patients, in whom thirteen episodes of hemarthrosis occurred. These authors observed that along with the property of increasing diffusion, hyaluronidase has the further effect on the joint of decreasing viscosity of synovial fluid, and increasing the permeability of the synovial membrane. As the result of these experiences, the authors recommend that, in addition to the usual treatment employed for acute hemorrhage into a joint, and if indicated, prompt infusion of the patient with plasma or fresh blood, hyaluronidase mixed with 1 per cent procaine be instilled into the affected joint.

Their procedure in brief is as follows: Under strict aseptic conditions a few cubic centimeters of joint fluid are aspirated and with the needle still in place, a preparation consisting of approximately 1,000 turbidity-reducing units of hyaluronidase mixed with 1 per cent procaine are instilled into the joint. Precaution is taken to instill into the joint a smaller volume of fluid than that which has been aspirated from it. These authors found that, as a rule, about 4 to 5 c.c. of instilled fluid is the usual quantity for major joints. Following this procedure, the joint is bandaged securely by means of an Ace bandage in order to exert external pressure. Such mechanical pressure increases diffusion and allows greater absorption to take place. No attempt is made to move the joint for twenty-four hours. If, at the end of the twenty-four-hour period, re-examination reveals significant evidence of blood still in the joint, the procedure is repeated. If the first treatment seems to have been adequate, the joint is rebandaged and observed for another twenty-four-hour period. In the experience of MacAusland and Gartland, most of the patients were in good condition at the end of forty-eight hours, and in many instances were allowed to go home. Full use of the joint was permitted and encouraged.

These authors include a detailed analysis of their cases in which the individual results are summarized: eight elbow joints, three ankle joints,

one knee joint, and one shoulder joint were treated in this manner. In eleven of the thirteen instances of hemarthrosis, rapid relief of pain and rapid restoration of normal range of motion were observed. In the majority of patients pain was greatly relieved by the end of the first twenty-four hours, and was absent completely by the end of the second twenty-four-hour period. As a general rule, the former range of motion of the joint was restored by the end of the forty-eight-hour period.

In a final critical analysis of the results in the thirteen episodes of hemarthrosis, eleven were classified as "result, satisfactory," one as "fair to satisfactory," and one as only "fair." The age range of these six patients was, respectively, 22, 15, 10, 9, 9, and 4 years. While no reactions to the use of hyaluronidase were observed, and no toxic manifestations were apparent in the six patients, the possible danger of procaine reaction must be kept in mind and anticipated.

The chief difficulty encountered was technical, that of joint aspiration itself in the younger and uncooperative patient. The authors urge that the young patient receive adequate sedation before aspiration of any joint is attempted.

Judging from the experience of these authors, it would appear that the enzymic substance, hyaluronidase, may have a definite place in the treatment of hemarthrosis in the patient with hemophilia. The extreme disability which usually follows repeated hemorrhage into the joint in the hemophilic patient is well known to the practicing physician. The long hospitalization necessary, and the prolonged and rather unsatisfactory care of joints crippled in this way, have been emphasized by orthopedic specialists for many years,[3, 4] and crippling of this type has been considered a major problem in the care of the patient with hemophilia.

The use of hyaluronidase in conditions other than hemophilia, such as sprains, fresh fractures, orthopedic problems resulting from edema and hemorrhage, hematoma, etc., is being studied by MacAusland and Gartland at the present time. A report concerning results in this broader field will be forthcoming in the near future.

Since the number of hemophilic persons in the United States, based on registration at the National Hemophilia Foundation, is of the order of forty thousand, such a substance as the enzyme, hyaluronidase, should prove of considerable clinical value in dealing with one of the serious complications of this disease.

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REFERENCES

1. MacAusland, W. R., Jr., and Gartland, J. J.: Treatment of Acute Hemophilic Hemarthrosis: A Report on the Use of Hyaluronidase, New England J. Med. **247**: 755, 1952.
2. Britton, R., and Habif, D.: Personal communication to MacAusland and Gartland.
3. Key, J. A.: Hemophilic Arthritis, Ann. Surg. **95**: 198, 1932.
4. Thomas, H. B.: Some Orthopaedic Findings in Ninety-eight Cases of Haemophilia, J. Bone & Joint Surg. **18**: 140, 1936.

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News and Notes

Lieutenant Colonel Leo J. Geppert, who has been chief of the pediatric service at the Brooke Army Hospital, Fort Sam Houston, Texas, for the last seven years, has been transferred to the Tokyo Army Hospital as chief of pediatrics and theater consultant for the Far East Command.

Dr. Alexander T. Martin has been elected president of the New York Academy of Medicine.

A fellowship in Pediatric Cardiology at the **University of Utah** is being offered for one year starting July 1, 1953. Both clinical and laboratory training in congenital and rheumatic heart disease will be given, and will include cardiac catheterization and angiocardiography. Applicants will be considered on the basis of former training and military status. The annual stipend will be $3,000 for an unmarried fellow and $3,600 for a married fellow. Applicants should write to Dr. L. George Veasy, Department of Pediatrics, University of Utah College of Medicine, Salt Lake General Hospital, Salt Lake City, Utah.

The **Cook County Graduate School of Medicine** announces a two-week intensive course on "The Diagnosis and Treatment of Congenital and of Rheumatic Heart Disease in Infants and Children," presented by Benjamin M. Gasul, M.D., and Egbert H. Fell, M.D., and associates, from May 18 to May 30, 1953. For a circular giving full information, write to: Registrar, Cook County Graduate School of Medicine, 707 South Wood St., Chicago, Ill.

Two-Week Postgraduate Course in General Pediatrics, Burnham Memorial Hospital for Children, Massachusetts General Hospital, Boston, under the auspices of the **Harvard Medical School** and direction of Dr. Allan M. Butler, professor of pediatrics, June 8 through June 20, 1953. Clinics providing a broad review of pediatrics emphasizing the new advances will be given daily from 9:00 A.M. to 4:30 P.M., by selected authorities from the pediatrics and specialty services of the Massachusetts General Hospital and the Children's Medical Center, Boston. For further information write Assistant Dean, Courses for Graduates, Harvard Medical School, 25 Shattuck Street, Boston, Mass.

The Institute of Experimental Medicine of the University of Montreal, of which Dr. Hans Selye is Director, issues each year a volume *Annual Reports on Stress*. Dr. Selye and the co-editor, Dr. Horava, request that authors of articles pertaining to "stress" and the so-called "adaptive hormones" as ACTH, corticoids, adrenergic substances, etc., supply the Institute with reprints of their articles for use in preparation of this annual report.

Book Reviews

Diseases of the Nervous System in Infancy, Childhood and Adolescence. Frank R. Ford, M.D., ed. 3, Springfield, Ill., 1952, Charles C Thomas, 1181 pages.

A new edition of Ford's *Diseases of the Nervous System*. Ford's text has become the standard reference text on diseases of the nervous system for the pediatrician. This new edition, the last was published in 1945, has been enlarged and much of it rewritten to keep it abreast of the many recent developments in diagnosis, and in treatment due to improved surgical techniques and the use of antibiotics which have taken place in recent years.

1952 Year Book of Pediatrics. Edited by Sydney S. Gellis, M.D., Chicago, 1952, Year Book Publishers, 423 pages. Price $5.50.

The *1952 Year Book of Pediatrics* is edited by Dr. Sydney S. Gellis of Boston, who has succeeded Drs. Poncher and Richmond of Chicago. It follows the usual formula covering pediatric literature from June, 1951, to May, 1952. Dr. Gellis has made an excellent selection from the American and a limited selection from foreign literature. We are happy to note the editorial comments started by Dr. Poncher have been continued. Dr. Gellis has also gone to specialists in certain

fields for comments on the importance of certain of the articles abstracted. The abstracts are clear and well written. The pediatric and medical journals have been generous in allowing the reproduction of a number of the illustrations in the original articles which add to the attractiveness of the book.

Human Milk. Yield, Proximate Principles and Inorganic Constituents. S. D. Morrison, B.Sc., 1952, Commonwealth Agricultural Bureaux, Farnham Royal, Slough, Bucks, 91 pages. Price $1.50.

In this monograph Morrison has collected and studied the important investigations on the yield and constituents of human milk except the vitamin content. Vitamin content was the subject of a special report by Kon and Mawson for the Medical Research Council in 1952. The study shows the wide variation in the nitrogen, fat, and lactose content of samples of human milk. It is interesting to note that the author could find little or no evidence that the yield of human milk varies with the water intake, contrary to the usual clinical impression and teaching, nor evidence of a diurnal rhythm. The monograph contains a wealth of statistical material for those interested in the chemical composition of human milk. One finishes the monograph with the feeling of how little exact knowledge we possess of the subject despite the numerous studies which have been made.

Angiocardiography. Charles T. Dotter, M.D., and Israel Steinberg, M.D., Annals of Roentgenology, Vol. XX, New York, 1951, Paul B. Hoeber, Inc., 304 pages. Price $16.00.

Angiocardiography has become a definite part of the more elaborate diagnostic armamentarium in the field of congenital heart disease. This book is a timely treatise, and the whole subject is handled in a very capable manner. There is an interesting historical section which reviews the claims to priority for originating the technique of angiocardiography and which goes back to 1929, but one of the co-authors claims priority for the procedure as it is practiced today.

The authors very carefully point out the inherent danger of angiocardiography in the cyanotic child and stress that the indications for such a procedure should be carefully considered. They also emphasize that when ordinary investigative means are sufficient to rule out surgery as a possible therapeutic approach, then angiocardiography should probably not be done.

The chief value of the book is in the excellent collection of photographs of the heart and great vessels as depicted by contrast medium and associated diagrams delineating the anatomical structures which are being visualized. The major part of the book is about the use of angiocardiography in congenital heart disease, although there are short sections about the use of this technique in acquired cardiac and pulmonary disease.

GOLDRING

Essentials of Infant Feeding for Physicians. Herman F. Meyer, M.D., Springfield, Ill., 1952, Charles C Thomas, 252 pages. Price $6.75.

This is an excellent practical text on infant feeding. The author has not attempted to go deeply into the metabolism of the infant, nor a lengthy discussion of the basic components which make up the infant's food. Rather he has in a direct way discussed infant feeding as it is practiced today in the United States. A very useful discussion and description of the multitude of proprietary or commercial preparations on the market is included, together with their special indications and uses. Tables XXXI, XXXII, and XXXIII on economic considerations, which give the cost per day of feedings based on evaporated and dairy milk as contrasted with the proprietary foods, are worthy of considerable study by the practitioner. The advice given by Dr. Meyer throughout is sane and practical, such, for example, as concerns the excessive use of vitamins. In referring to the multiplicity of foods presented to the practitioner, the advice to choose one or two products in each category and become familiar with their clinical use is very sound advice. The text includes a tremendous amount of data regarding infant diet and foods in current use which will be of great value to the pediatrician, and which make it a very handy text to have in the working library in the office. In the opinion of the reviewer it is a needed text on infant feeding, as there is nothing quite like it, and it contains a wealth of material for rapid reference.

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Editor's Column

EARLY HOME CARE OR INSTITUTION FOR THE RETARDED CHILD

A FEW weeks ago the following letter was received from the Director of the Lochland School for retarded children at Geneva, New York.

Dear Dr. Veeder:

For approximately twenty years I have conducted a school for retarded children. During this period I have been increasingly disturbed by the attitude of many members of the medical profession which complicates for parents the problem of accepting their retarded children. I refer to the current practice of advising parents of a child whose development is slow to place him in an institution as early as possible.

The reasons usually given for this early separation are:

(1) The extra care he requires often complicates the family life.

(2) Later separation will be more difficult for both parents and child.

(3) His presence in the home is harmful to siblings.

My experience has convinced me that parents who keep such a child at home as a loved member of the family until he is three or four years of age are better able to accept his handicap and relinquish the later care of him with less pain because they have the satisfaction of having given him several years of tender care.

The siblings also need to know their little brother during infancy and this relationship with him will help them to accept his handicap with sympathy and understanding when it is explained to them in later years. I am convinced that this problem can be handled without trauma to either child if thoughtfully planned.

We, at Lochland, find that children who have had several years of loving care at home are happier, better adjusted children than the ones who have been deprived of these experiences.

We frequently are asked to take infants whose parents have been advised to put them in a school, but if the baby can be cared for at home affectionately without too great a strain on the family, we recommend that placement be delayed for several years. We are not referring here to the baby who shows gross physical stigmas but to those who show a developmental lag and possibly mild cases of mongolism. This procedure does not deprive the family of the responsibility of loving and caring for the baby during its first years and helps to reduce the feeling of guilt which derives from rejecting him at an early age. We also feel that retarded children need the assurance of the love of their families and contact with them through letters and visits.

May I ask that this question of early placement be reappraised by your branch of the medical profession at an early conference.

Sincerely yours,
FLORENCE H. STEWART
Director

The Editor was somewhat puzzled by this rather general criticism of the attitude of the medical profession on the question of early home versus institutional care for the retarded child, as for many years he had practiced and taught early home care although for somewhat different reasons than given in the letter. Wondering if he was out of step with "current practice," to use the term in the letter, a copy was sent to four members of the Editorial Board who had been in practice for enough years to have had to face the problem many times, asking for their comment.

The attitude of the Editor has been that, aside from infants with gross stigmas of idiocy, an infant or young

child in whom retardation is suspected is best cared for at home. First, as Dr. Shaw in his comment below points out, there is need for extreme caution in prognosticating the ultimate degree of mentality in a seemingly retarded infant or young child. Years ago the Editor learned his lesson when he agreed with the diagnosis of mental retardation in a 6-month-old infant made by two other pediatricians, only to watch her over the years stand high in school and make an excellent record in college. The second is that in his experience no one will have the necessary patience in training, or make the effort to bring out the potential possibilities of development better than the mother of the child. He has seen remarkable development take place, far beyond expectations in some of these children, and fully believes that they would have lapsed into a vegetative existence if they had been institutionalized in infancy. Later the parents often recognized that a stage was reached where the child required a type of training they were no longer qualified to give, and an institution became automatic. As a matter of fact, one of the chief problems involved in home versus institutional care has been the economic one—a problem that has become more difficult in recent years. The rate, for example, in the Lochland School is $3,600 to $6,000 a year. In many parts of the country state institutions are understaffed and overcrowded, and frequently there is a long waiting list.

The members of the Editorial Board to whom the letter was referred feel that the request that "the question of early placement be reappraised by your branch of the medical profession" deserves thought and consideration. The following comments have been made.

Comment by Dr. Edward Shaw of San Francisco:

The letter is interesting and deserves comment and discussion, for it concerns matters which are part of the experience of every practicing pediatrician and which engage a greater share of his time as he becomes ripened in practice.

I believe that the idea that the markedly subnormal child, especially the mongol, should be separated from the family at the earliest possible moment really stems from Dr. Brennemann who held most vociferously that it was the responsibility of the pediatrician to recognize this condition in early infancy and practically to demand that the mother should not take the child home from the hospital with her but should place it immediately in an institution.

It has always seemed to me that this point of view was an extremely arrogant one in which the pediatrician admitted no possibility of ever being wrong in his diagnosis, or incorrect in his opinion of the best solution for the involved family. Even in frank mongolism there is considerable difference in degree; some of these children progress to a certain point before they level off in their development and most pediatricians will be able to recall certain cases in which physical characteristics pointed to mongolism but in which the developmental pattern only gradually sustained the diagnosis indicated by the physical characteristics. I recall one man of distinguished attainments whose appearance was so mongoloid that I always wondered how he had escaped an institution in his early years of life.

It has seemed kinder to me and less arrogant to permit the family gradually to realize the limitations in intelligence of a defective child. This does not justify the pediatrician in withholding his misgivings, suspicions, or certainties regarding the ultimate prognosis, but allows the family to share in the final decision which recognizes the degree of subnormality and the problem which applies to siblings and to the rest of the family.

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The situation is simpler in mongolism in which the physical characteristics are so often unmistakable but is much more complicated with the brain-damaged child from one cause or another in which it may be very difficult to predict the final attainments. Parents are certainly much more at peace with the situation if they have made an honest effort to overcome an initial handicap by providing the normal care of infancy and early childhood so that final institutionalization does not make them feel guilty and unhappy. So often there is no test which can be applied in early infancy to establish an absolutely dismal prognosis and parents should be encouraged to help these children along in the best possible way in a normal family relationship. If the problem is discussed with them frankly and openly a decision can be arrived at through consulting with the pediatrician and a time selected to place the child in an institution which will not penalize other normal members of the family. I thoroughly agree that children in a family will profit from trying to help a member of the family overcome his handicaps and when eventual separation from the family is desirable it is usually possible to effect this without too much pain.

It is my own practice to try to explain to the parents exactly what I see in a child which points to subnormal development. Very often they are reluctant to accept this opinion and sometimes they will hastily flee from the physician who suggests that anything is wrong. I usually state that I sincerely hope that my opinion that a child is seriously retarded is in error and only careful watching will determine whether or not it is correct.

There are, of course, parents who are completely unwilling to admit that a child is subnormal at a time when there is no longer any question about this. In such a situation it is the responsibility of the pediatrician to express his opinions most forcibly, particularly if there are other children in the family who are being jeopardized by the drag of the subnormal child. I have occasionally seen children who were traumatized throughout their entire childhood by having to carry along a sibling in their usual activities where the parents were completely unwilling to admit that the child was subnormal. This is probably the only reason for the assertion that every subnormal child should be separated from his family at the earliest possible moment.

The economics of the situation is another matter. There are very few places where a small infant can be kept by the average family. To place these children in state homes necessitates a certain amount of delay and I think this is a good thing for the family must then assume the early care of the child whether they want to or not.

Comment by Dr. Stewart Clifford of Boston:

A study of the letter reveals that in this region there would be found quite complete medical agreement with Miss Stewart's general thesis. However, the letter suggests that she is not clear in her own mind as to how certain important problems should be handled. The author qualifies her recommendation that placement in an institution be delayed for several years *if it can be done without too great a strain on the family.* This is where personal judgment enters and in an individual case there might well be an honest difference of opinion between the physician and Miss Stewart.

Miss Stewart implies that babies with gross physical stigmas should be institutionalized early—there is no disagreement with medical opinion here.

She feels that the babies who show only a developmental lag should be followed at home until the need for institutional care becomes obvious—certainly there is no disagreement with accepted medical opinion here.

However, a positive opinion on the important group of babies where there is wide variation in medical thinking as to the ideal management is avoided. This is the group of mongols. She states that *possibly the mild cases of mongolism should be cared for at home for several years.* I personally make every effort to have the obvious mongolian baby go to an institution from the obstetric hospital. When this is not possible, I try to have him institutionalized by the time he is two to four years of age. The group of physicians who are in charge of our state institutions take sharp issue with this policy of immediately institutionalizing mongol babies from the obstetric hospital. I am not sure as to the best policy for this

group, and Miss Stewart is apparently in doubt about this too.

In passing, I do not think the statement that "children who have been cared for in the family until three or four years of age are happier, better adjusted children than the ones who have been deprived of these experiences," can be accepted. They are probably not comparable groups since by natural selection the most severe and unfavorable cases would come to the institution at an earlier age.

I do not believe the blanket condemnation of the current practices of the medical profession is justified. The whole subject cannot be lumped together and dogmatic rules established. Mental retardation can be of multiple causes—each type must be considered separately. Furthermore, they must be considered as to the age at which the positive diagnosis can be established. In some cases, it is at birth—in others, anoxic damage can be suspected at birth but it may take years before the true picture is evident.

If we can define the group about which we are talking, then there is not much difference of opinion encountered.

Comment by Dr. Lee Hill of Des Moines:

A few years ago I would have answered your inquiry about Miss Stewart's lettter quite differently from the way I am doing now. Perhaps it is the mellowness of advancing years, but more likely it is the result of information gained from long experience which has resulted in my changing views. So far as mongols go, I have always felt it was best, if the condition could be diagnosed at birth, to make the separation at that time rather than later when it becomes much more difficult for parents to break off the attachment which is bound to develop. Andy Aldrich and I used to talk about this problem, and I know he followed this routine, whenever it was possible.

The cerebral palsied child, however, is entirely a different story. I am sure many of us in the past urged institutionalization of children who appeared to be hopelessly damaged when this was not actually so. Today I have many such children under my care where I have advised the parents to keep them at home until it has been proved beyond question that any degree of useful mentality cannot be expected. I am sure my thinking in this respect has been tempered by the interest which has sprung up in all quarters over cerebral palsied children.

I think the letter brings up a most important problem. As I said earlier, some years back it was my practice to refer all mentally damaged children to institutions as soon as possible, but, in recent years, I find myself much more frequently placing the possibilities before the parents and letting them make their own decision. I still recommend early institutionalization for mongols and hopelessly brain-damaged children.

Comment by Dr. Harry Bakwin of New York:

In my opinion the problem of early institutionalizing a defective child must be decided individually. In the case of young parents, if a positive diagnosis of mental deficiency can be made at birth, as in the case of a mongol, I generally advise institutional or foster-home care if it can be arranged. There is obviously no point in advising institutional or foster-home care if this is, for any reason, impossible.

When hitherto childless parents in their middle years produce a defective baby, the situation is much different. Many parents have a strong sense of duty. Often they do not plan to have more children and prefer a defective child to none at all. It has been my practice here not to interfere but rather to reinforce any decision which the parents seem inclined to make.

When parents who have already had several children have a defective child, a careful judgment is necessary on the basis of the desires of the parents, the age difference between the defective baby and the older siblings, the parents' appreciation of the effect of having a defective baby in the home on the older children. Though the effect on the older children is generally an adverse one, having a defective baby in the home can under certain circumstances be an ennobling experience for them. The parents' behavior toward the unfortunate member of the household may serve as a model for the older children and may engender in them a similar helpful attitude toward less fortunate members of society.

If the attitude and practice of these five pediatricians in different parts of the country reflect the general attitude of physicians to the question raised, it does not seem that the general criticism in the letter is justified.

As pointed out in the comments dogmatic rules cannot be established. Each case must be individualized and it is just here that much thought and wise counseling must be given by the physician to whom the parents turn for help in their tragedy. Many factors must be taken into consideration. Among these are the degree of retardation, the attitude of the parents toward the child, the social background of the family, the physical facilities of the home, the question of siblings, the economic situation of the family, and the availability of satisfactory institutions. These are far better known to the physician than to institutional authorities.

Perhaps some of our readers, or those in charge of training in institutions, can help clarify the problem.

ACRODYNIA

THE acrodynic syndrome is one of the most bizarre pediatric diseases. There has been considerable speculation as to the etiology and a number of hypotheses have been suggested. In last month's issue Cheek of Australia, where the disease is more prevalent than in this country, discussed the clinical picture and reviewed the studies on the alternations in physiology which occur in the course of the disease. Some of the changes are similar to those found in the group of "stress" conditions involving adrenal function.

In this month's issue Warkany reviews the relationship between mercury and acrodynia which he pointed out several years ago, and presents new and convincing evidence that mercury is the "most frequent causative agent of the acrodynic syndrome" as it is seen in this country and Europe. There are a number of unanswered questions in this relationship, as why mercury produces acrodynia in one child and not in another. Perhaps the findings of Cheek and Warkany may be interrelated in this selectivity.

Warkany's work places acrodynia in the group of diseases which are largely preventable. He points out that acrodynia has chiefly followed the use of mercury in "teething powders," as a vermifuge, and in the treatment of impetigo. There are other drugs available that not only will obviate the use of mercury, but are superior to mercury for these indications.